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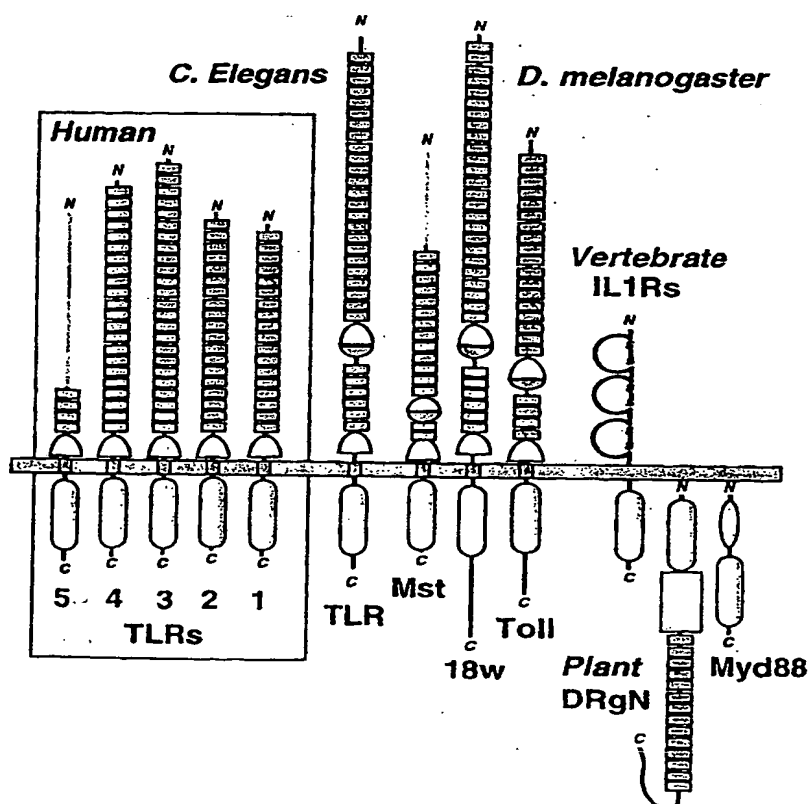
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(54) Title: HUMAN TOLL-LIKE RECEPTOR PROTEINS, RELATED REAGENTS AND METHODS

## (57) Abstract

Nucleic acids encoding nine human receptors, designated DNAX Toll-like receptors 2-10 (DTLR2-10), homologous to the Drosophila Toll receptor and the human IL-1 receptor, purified DTLR proteins and fragments thereof, mono-/polyclonal antibodies against these receptors, and methods for diagnostic and therapeutic use.



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HUMAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

This filing claims priority from U.S. Patent  
5 Applications USSN 60/044,293, filed May 7, 1997; USSN  
60/072,212, filed January 22, 1998; and USSN 60/076,947,  
filed March 5, 1998, each of which is incorporated herein  
by reference.

10 FIELD OF THE INVENTION

The present invention relates to compositions and  
methods for affecting mammalian physiology, including  
morphogenesis or immune system function. In particular,  
it provides nucleic acids, proteins, and antibodies which  
15 regulate development and/or the immune system.  
Diagnostic and therapeutic uses of these materials are  
also disclosed.

BACKGROUND OF THE INVENTION

20 Recombinant DNA technology refers generally to  
techniques of integrating genetic information from a  
donor source into vectors for subsequent processing, such  
as through introduction into a host, whereby the  
transferred genetic information is copied and/or  
25 expressed in the new environment. Commonly, the genetic  
information exists in the form of complementary DNA  
(cDNA) derived from messenger RNA (mRNA) coding for a  
desired protein product. The carrier is frequently a  
plasmid having the capacity to incorporate cDNA for later  
30 replication in a host and, in some cases, actually to  
control expression of the cDNA and thereby direct  
synthesis of the encoded product in the host.

For some time, it has been known that the mammalian  
immune response is based on a series of complex cellular  
35 interactions, called the "immune network". Recent  
research has provided new insights into the inner  
workings of this network. While it remains clear that

much of the immune response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play critical roles in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders.

Lymphokines apparently mediate cellular activities in a variety of ways. They have been shown to support the proliferation, growth, and/or differentiation of pluripotential hematopoietic stem cells into vast numbers of progenitors comprising diverse cellular lineages which make up a complex immune system. Proper and balanced interactions between the cellular components are necessary for a healthy immune response. The different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

Cell lineages especially important to the immune response include two classes of lymphocytes: B-cells, which can produce and secrete immunoglobulins (proteins with the capability of recognizing and binding to foreign matter to effect its removal), and T-cells of various subsets that secrete lymphokines and induce or suppress the B-cells and various other cells (including other T-cells) making up the immune network. These lymphocytes interact with many other cell types.

Another important cell lineage is the mast cell (which has not been positively identified in all mammalian species), which is a granule-containing connective tissue cell located proximal to capillaries throughout the body. These cells are found in especially



high concentrations in the lungs, skin, and gastrointestinal and genitourinary tracts. Mast cells play a central role in allergy-related disorders, particularly anaphylaxis as follows: when selected  
5 antigens crosslink one class of immunoglobulins bound to receptors on the mast cell surface, the mast cell degranulates and releases mediators, e.g., histamine, serotonin, heparin, and prostaglandins, which cause allergic reactions, e.g., anaphylaxis.

10 Research to better understand and treat various immune disorders has been hampered by the general inability to maintain cells of the immune system in vitro. Immunologists have discovered that culturing many of these cells can be accomplished through the use of T-  
15 cell and other cell supernatants, which contain various growth factors, including many of the lymphokines.

The interleukin-1 family of proteins includes the IL-1 $\alpha$ , the IL-1 $\beta$ , the IL-1RA, and recently the IL-1 $\gamma$  (also designated Interferon-Gamma Inducing Factor, IGIF).  
20 This related family of genes have been implicated in a broad range of biological functions. See Dinarello (1994) FASEB J. 8:1314-1325; Dinarello (1991) Blood 77:1627-1652; and Okamura, et al. (1995) Nature 378:88-91.

25 In addition, various growth and regulatory factors exist which modulate morphogenetic development. This includes, e.g., the Toll ligands, which signal through binding to receptors which share structural, and mechanistic, features characteristic of the IL-1  
30 receptors. See, e.g., Lemaitre, et al. (1996) Cell 86:973-983; and Belvin and Anderson (1996) Ann. Rev. Cell & Devel. Biol. 12:393-416.

From the foregoing, it is evident that the discovery and development of new soluble proteins and their  
35 receptors, including ones similar to lymphokines, should contribute to new therapies for a wide range of degenerative or abnormal conditions which directly or

indirectly involve development, differentiation, or function, e.g., of the immune system and/or hematopoietic cells. In particular, the discovery and understanding of novel receptors for lymphokine-like molecules which enhance or potentiate the beneficial activities of other lymphokines would be highly advantageous. The present invention provides new receptors for ligands exhibiting similarity to interleukin-1 like compositions and related compounds, and methods for their use.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic comparison of the protein architectures of *Drosophila* and human DTLRs, and their relationship to vertebrate IL-1 receptors and plant disease resistance proteins. Three *Drosophila* (Dm) DTLRs (Toll, 18w, and the Mst ORF fragment) (Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399; Chiang and Beachy (1994) Mech. Develop. 47:225-239; Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783; and Eldon, et al. (1994) Develop. 120:885-899) are arrayed beside four complete (DTLRs 1-4) and one partial (DTLR5) human (Hu) receptors. Individual LRRs in the receptor ectodomains that are flagged by PRINTS (Attwood, et al. (1997) Nucleic Acids Res. 25:212-217) are explicitly noted by boxes; 'top' and 'bottom' Cys-rich clusters that flank the C- or N-terminal ends of LRR arrays are respectively drawn by apposed half-circles. The loss of the internal Cys-rich region in DTLRs 1-5 largely accounts for their smaller ectodomains (558, 570, 690, and 652 aa, respectively) when compared to the 784 and 977 aa extensions of Toll and 18w. The incomplete chains of DmMst and HuDTLR5 (519 and 153 aa ectodomains, respectively) are represented by dashed lines. The intracellular signaling module common to DTLRs, IL-1-type receptors (IL-1Rs), the intracellular protein Myd88, and the tobacco disease resistance gene N product (DRgN) is indicated below the membrane. See, e.g., Hardiman, et

al. (1996) Oncogene 13:2467-2475; and Rock, et al. (1998) Proc. Nat'l Acad. Sci. USA 95:588-. Additional domains include the trio of Ig-like modules in IL-1Rs (disulfide-linked loops); the DRgN protein features an NTPase domain (box) and Myd88 has a death domain (black oval).

Figures 2A-2B show conserved structural patterns in the signaling domains of Toll- and IL-1-like cytokine receptors, and two divergent modular proteins. Figure 2A shows a sequence alignment of the common TH domain.

DTLRs are labeled as in Figure 1; the human (Hu) or mouse (Mo) IL-1 family receptors (IL-1R1-6) are sequentially numbered as earlier proposed (Hardiman, et al. (1996) Oncogene 13:2467-2475); Myd88 and the sequences from tobacco (To) and flax, *L. usitatissimum* (Lu), represent C- and N-terminal domains, respectively, of larger, multidomain molecules. Ungapped blocks of sequence (numbered 1-10) are boxed. Triangles indicate deleterious mutations, while truncations N-terminal of the arrow eliminate bioactivity in human IL-1R1 (Heguy, et al. (1992) J. Biol. Chem. 267:2605-2609). PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310) secondary structure predictions of  $\alpha$ -helix (H),  $\beta$ -strand (E), or coil (L) are marked. The amino acid shading scheme depicts chemically similar residues: hydrophobic, acidic, basic, Cys, aromatic, structure-breaking, and tiny. Diagnostic sequence patterns for IL-1Rs, DTLRs, and full alignment (ALL) were derived by Consensus at a stringency of 75%. Symbols for amino acid subsets are (see internet site for detail): o, alcohol; l, aliphatic; ., any amino acid; a, aromatic; c, charged; h, hydrophobic; -, negative; p, polar; +, positive; s, small; u, tiny; t, turnlike. Figure 2B shows a topology diagram of the proposed TH  $\beta/\alpha$  domain fold. The parallel  $\beta$ -sheet (with  $\beta$ -strands A-E as yellow triangles) is seen at its C-terminal end;  $\alpha$ -helices (circles labeled 1-5) link the  $\beta$ -strands; chain connections are to the front (visible) or

back (hidden). Conserved, charged residues at the C-end of the  $\beta$ -sheet are noted in gray (Asp) or as a lone black (Arg) residue (see text).

Figure 3 shows evolution of a signaling domain superfamily. The multiple TH module alignment of Figure 2A was used to derive a phylogenetic tree by the Neighbor-Joining method (Thompson, et al. (1994) Nucleic Acids Res. 22:4673-4680). Proteins labeled as in the alignment; the tree was rendered with TreeView.

Figures 4A-4D show FISH chromosomal mapping of human DTLR genes. Denatured chromosomes from synchronous cultures of human lymphocytes were hybridized to biotinylated DTLR cDNA probes for localization. The assignment of the FISH mapping data (left, Figures 4A, DTLR2; 4B, DTLR3; 4C, DTLR4; 4D, DTLR5) with chromosomal bands was achieved by superimposing FISH signals with DAPI banded chromosomes (center panels). Heng and Tsui (1994) Meth. Molec. Biol. 33:109-122. Analyses are summarized in the form of human chromosome ideograms (right panels).

Figures 5A-5F show mRNA blot analyses of Human DTLRs. Human multiple tissue blots (He, heart; Br, brain; Pl, placenta; Lu, lung; Li, liver; Mu, muscle; Ki, kidney; Pn, Pancreas; Sp, spleen; Th, thymus; Pr, prostate; Te, testis; Ov, ovary, SI, small intestine; Co, colon; PBL, peripheral blood lymphocytes) and cancer cell line (promyelocytic leukemia, HL60; cervical cancer, HELAS3; chronic myelogenous leukemia, K562; lymphoblastic leukemia, Molt4; colorectal adenocarcinoma, SW480; melanoma, G361; Burkitt's Lymphoma Raji, Burkitt's; colorectal adenocarcinoma, SW480; lung carcinoma, A549) containing approximately 2  $\mu$ g of poly(A)<sup>+</sup> RNA per lane were probed with radiolabeled cDNAs encoding DTLR1 (Figures 5A-5C), DTLR2 (Figure 5D), DTLR3 (Figure 5E), and DTLR4 (Figure 5F) as described. Blots were exposed to X-ray film for 2 days (Figures 5A-5C) or one week (Figure 5D-5F) at -70° C with intensifying screens. An

anomalous 0.3 kB species appears in some lanes; hybridization experiments exclude a message encoding a DTLR cytoplasmic fragment.

SUMMARY OF THE INVENTION

5       The present invention is directed to nine novel related mammalian receptors, e.g., human, Toll receptor like molecular structures, designated DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, and DTLR10, and their biological activities. It includes nucleic acids  
10       coding for the polypeptides themselves and methods for their production and use. The nucleic acids of the invention are characterized, in part, by their homology to cloned complementary DNA (cDNA) sequences enclosed herein.

15       In certain embodiments, the invention provides a composition of matter selected from the group of: a substantially pure or recombinant DTLR2 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID  
20       NO: 4; a natural sequence DTLR2 of SEQ ID NO: 4; a fusion protein comprising DTLR2 sequence; a substantially pure or recombinant DTLR3 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 6; a natural  
25       sequence DTLR3 of SEQ ID NO: 6; a fusion protein comprising DTLR3 sequence; a substantially pure or recombinant DTLR4 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 26; a natural sequence  
30       DTLR4 of SEQ ID NO: 26; a fusion protein comprising DTLR4 sequence; a substantially pure or recombinant DTLR5 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 10; a natural sequence DTLR5 of SEQ ID NO:  
35       10; and a fusion protein comprising DTLR5 sequence.

      In other embodiments, the invention provides a composition of matter selected from the group of: a

substantially pure or recombinant DTLR6 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 12; a natural sequence DTLR6 of SEQ ID NO: 12; a fusion protein comprising DTLR6 sequence; a substantially pure or recombinant DTLR7 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 16 or 18 or; a natural sequence DTLR7 of SEQ ID NO: 16 or 18; a fusion protein comprising DTLR7 sequence; a substantially pure or recombinant DTLR8 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 32; a natural sequence DTLR8 of SEQ ID NO: 32; a fusion protein comprising DTLR8 sequence; a substantially pure or recombinant DTLR9 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 22; a natural sequence DTLR9 of SEQ ID NO: 22; and a fusion protein comprising DTLR9 sequence; a substantially pure or recombinant DTLR10 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 34; a natural sequence DTLR10 of SEQ ID NO: 34; and a fusion protein comprising DTLR10 sequence.

Preferably, the substantially pure or isolated protein comprises a segment exhibiting sequence identity to a corresponding portion of a DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR 7, DTLR8, DTLR9, or DTLR10, wherein: the homology is at least about 90% identity and the portion is at least about 9 amino acids; the homology is at least about 80% identity and the portion is at least about 17 amino acids; or the homology is at least about 70% identity and the portion is at least about 25 amino acids. In specific embodiments, the composition of matter: is DTLR2, which comprises a mature sequence of SEQ ID NO: 4; or exhibits a post-translational+

modification pattern distinct from natural DTLR2; is DTLR3, which comprises a mature sequence of SEQ ID NO: 6; or exhibits a post-translational modification pattern distinct from natural DTLR3; is DTLR4, which: comprises a  
5 mature sequence of SEQ ID NO: 26; or exhibits a post-translational modification pattern distinct from natural DTLR4; or is DTLR5, which: comprises the complete sequence of SEQ ID NO: 10; or exhibits a post-translational modification pattern distinct from natural  
10 DTLR5; or is DTLR6, which comprises a mature sequence of SEQ ID NO: 12; or exhibits a post-translational modification pattern distinct from natural DTLR6; is DTLR7, which comprises a mature sequence of SEQ ID NO: 16 or 18; or exhibits a post-translational modification  
15 pattern distinct from natural DTLR7; is DTLR8, which: comprises a mature sequence of SEQ ID NO: 32; or exhibits a post-translational modification pattern distinct from natural DTLR8; or is DTLR9, which: comprises the complete sequence of SEQ ID NO: 22; or exhibits a post-  
20 translational modification pattern distinct from natural DTLR9; or is DTLR10, which: comprises the complete sequence of SEQ ID NO: 34; or exhibits a post-translational modification pattern distinct from natural DTLR10; or the composition of matter may be a protein or  
25 peptide which: is from a warm blooded animal selected from a mammal, including a primate, such as a human; comprises at least one polypeptide segment of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34; exhibits a plurality of portions exhibiting said identity; is a  
30 natural allelic variant of DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9,  
35 or DTLR10; exhibits a sequence identity at least about 90% over a length of at least about 20 amino acids to a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6; exhibits at

least two non-overlapping epitopes which are specific for a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; exhibits a sequence identity at least about 90% over a length of at least about 20 amino acids to a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10; is glycosylated; has a molecular weight of at least 100 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence.

Other embodiments include a composition comprising: a sterile DTLR2 protein or peptide; or the DTLR2 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR3 protein or peptide; or the DTLR3 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR4 protein or peptide; or the DTLR4 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR5 protein or peptide; or the DTLR5 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR6 protein or peptide; or the DTLR6 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR7 protein or peptide; or the DTLR7 protein or peptide and a carrier,



wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR8 protein or peptide; or the DTLR8 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR9 protein or peptide; or the DTLR9 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a sterile DTLR10 protein or peptide; or the DTLR10 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

In certain fusion protein embodiments, the invention provides a fusion protein comprising: mature protein sequence of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another receptor protein.

Various kit embodiments include a kit comprising a DTLR protein or polypeptide, and: a compartment comprising the protein or polypeptide; and/or instructions for use or disposal of reagents in the kit.

Binding compound embodiments include those comprising an antigen binding site from an antibody, which specifically binds to a natural DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10 protein, wherein: the protein is a primate protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34; is raised against a mature

DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9 or DTLR10; is raised to a purified human DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9 or DTLR10; is immunoselected; is a polyclonal antibody; binds to a  
5 denatured DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9 or DTLR10; exhibits a  $K_d$  to antigen of at least 30  $\mu$ M; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or  
10 fluorescent label. A binding composition kit often comprises the binding compound, and: a compartment comprising said binding compound; and/or instructions for use or disposal of reagents in the kit. Often the kit is capable of making a qualitative or quantitative analysis.

15 Other compositions include a composition comprising: a sterile binding compound, or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral  
20 administration.

Nucleic acid embodiments include an isolated or recombinant nucleic acid encoding a DTLR2-10 protein or peptide or fusion protein, wherein: the DTLR is from a mammal; or the nucleic acid: encodes an antigenic peptide  
25 sequence of of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34; encodes a plurality of antigenic peptide sequences of of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34; exhibits at least about 80% identity to a natural cDNA encoding said segment; is an expression  
30 vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a mammal, including a primate; comprises a natural full length  
35 coding sequence; is a hybridization probe for a gene encoding said DTLR; or is a PCR primer, PCR product, or mutagenesis primer. A cell, tissue, or organ comprising

such a recombinant nucleic acid is also provided. Preferably, the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell. Kits are provided comprising such nucleic acids, and: a compartment comprising said nucleic acid; a compartment further comprising a primate DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9 or DTLR10 protein or polypeptide; and/or instructions for use or disposal of reagents in the kit. Often, the kit is capable of making a qualitative or quantitative analysis.

Other embodiments include a nucleic acid which: hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 3; hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 5; hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 25; hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 9; hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 11; hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 15 or 17; hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 31; hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 21; hybridizes under wash conditions of 30° C and less than 2 M salt to SEQ ID NO: 33; exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DTLR2 DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9 or DTLR10.

Preferably, such nucleic acid will have such properties, wherein: wash conditions are at 45° C and/or 500 mM salt; or the identity is at least 90% and/or the stretch is at least 55 nucleotides. More preferably, the wash conditions are at 55° C and/or 150 mM salt; or the identity is at least 95% and/or the stretch is at least 75 nucleotides.

The invention also provides a method of modulating physiology or development of a cell or tissue culture cells comprising contacting the cell with an agonist or antagonist of a mammalian DTLR2, DTLR3, DTLR4, DTLR5,  
5 DTLR6, DTLR7, DTLR8, DTLR9, or DTLR10.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

##### I. General

10 The present invention provides the amino acid sequence and DNA sequence of mammalian, herein primate DNAX Toll like receptor molecules (DTLR) having particular defined properties, both structural and biological. These have been designated herein as DTLR2,  
15 DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, and DTLR10, respectively, and increase the number of members of the human Toll like receptor family from 1 to 10. Various cDNAs encoding these molecules were obtained from primate, e.g., human, cDNA sequence libraries. Other  
20 primate or other mammalian counterparts would also be desired.

Some of the standard methods applicable are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring  
25 Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and periodic supplements) Current Protocols  
30 in Molecular Biology, Greene/Wiley, New York; each of which is incorporated herein by reference.

A complete nucleotide and corresponding amino acid sequence of a human DTLR1 coding segment is shown in SEQ ID NO: 1 and 2. See also Nomura, et al. (1994) DNA Res  
35 1:27-35. A complete nucleotide and corresponding amino acid sequence of a human DTLR2 coding segment is shown in SEQ ID NO: 3 and 4. A complete nucleotide and

corresponding amino acid sequence of a human DTLR3 coding segment is shown in SEQ ID NO: 5 and 6. A complete nucleotide and corresponding amino acid sequence of a human DTLR4 coding segment is shown in SEQ ID NO: 7 and 8. An alternate nucleic acid and corresponding amino acid sequence of a human DTLR4 coding segment is provided in SEQ ID NO: 25 and 26. A partial nucleotide and corresponding amino acid sequence of a human DTLR5 coding segment is shown in SEQ ID NO: 9 and 10. A complete nucleotide and corresponding amino acid sequence of a human DTLR6 coding segment is shown in SEQ ID NO: 11 and 12 and a partial sequence of a mouse DTLR6 is provided in SEQ ID NO: 13 and 14. Additional mouse DTLR6 sequence is provided in SEQ ID NO: 27 and 29 (nucleotide sequence) and SEQ ID NO: 28 and 30 (amino acid sequence). Partial nucleotide (SEQ ID NO: 15 and 17) and corresponding amino acid sequence (SEQ ID NO: 16 and 18) of a human DTLR7 coding segment is also provided. Partial nucleotide and corresponding amino acid sequence of a human DTLR8 coding segment is shown in SEQ ID NO: 19 and 20. A more complete nucleotide and corresponding amino acid sequence of a human DTLR coding segment is shown in SEQ ID NO: 31 and 32. Partial nucleotide and corresponding amino acid sequence of a human DTLR9 coding segment is shown in SEQ ID NO: 21 and 22. Partial nucleotide and corresponding amino acid sequence of a human DTLR10 coding segment is shown in SEQ ID NO: 23 and 24. More complete nucleotide and corresponding amino acid sequence of a human DTLR10 coding segment is shown in SEQ ID NO: 33 and 34. A partial nucleotide sequence for a mouse DTLR10 coding segment is provided in SEQ ID NO: 35.

Table 1: Comparison of intracellular domains of human DTLRs.  
 DTLR1 is SEQ ID NO: 2; DTLR2 is SEQ ID NO: 4; DTLR3 is SEQ ID NO: 6; DTLR4 is SEQ ID NO: 8; DTLR5 is SEQ ID NO: 10; and DTLR6 is SEQ ID NO: 12. Particularly important and conserved, e.g., characteristic, residues correspond, across the DTLRs, to SEQ ID NO: 18 residues tyr10-tyr13; trp26; cys46; trp52; pro54-gly55; ser69; lys71; trp134-pro135; and phe144-trp145.

10	DTLR1	QRNLQFHAFISYSGHD---SFVVKNE LLPNLEKEG-----MQICLHERNF
	DTLR9	KENLQFHAFISYSEHD---SAWVKSELVPYLEKED-----IQICLHERNF
	DTLR8	-----NELIPNLEKEDGS---ILICLYESYF
	DTLR2	SRNICYDAFVSYSERD---AYWVENLMVQELFNFPNPP---FKLCLHKRDF
	DTLR6	SPDCCYDAFIVYDTKDPVTEWVLAELVAKLEDPREK---HFNLCLLEERDW
	DTLR7	TSQTFYDAYISYDTKDASVTDWVINELRYHLEESRDK---NVLLCLEERDW
15	DTLR10	EDALPYDAFVVFDTKTXSAVADWVYNELRGQLEECRGRW-ALRLCLEERDW
	DTLR4	RGENIYDAFVIYSSQD---EDWVRNELVKNLEEGVPP---FQLCLHYRDF
	DTLR5	PDMYKYDAYLCFSSKD---FTWVQNALLKHLDTQYSDQNRFNLCFEERDF
	DTLR3	TEQFEYAAAYIIHAYKD---KDWVWEHFSSMEKEDQS----LKFCLEERDF
		: . . . : *
20	DTLR1	VPGKSIVENIITC-IEKSYKSIFVLSPNFVQSEWCH-YELYFAHHNLFHE
	DTLR9	VPGKSIVENIINC-IEKSYKSIFVLSPNFVQSEWCH-YELYFAHHNLFHE
	DTLR8	DPGKSISENIVSF-IEKSYKSIFVLSPNFVQNEWCH-YEFYFAHHNLFHE
	DTLR2	IPGKWIIDNIIDS-IEKSHKTVFVLSENFKSEWCK-YELDFSHFRLFEE
25	DTLR6	LPGQPVLENLSQS-IQLSKKTVFVMTDKYAKTENFK-IAFYLSHQRLMDE
	DTLR7	DPLGLAIDNLMQS-INQSKKTVFVLTKKYAKSWNFK-TAFYLLXQLRMGE
	DTLR10	LPGKTLFENLWAS-VYGSRKTLFVLAHTDRVSGLLR-AIFLLAQORLLE-
	DTLR4	IPGVAIAANIIEHGFHKSRKVIIVVVSQHFIQSRWCI-FEYETIAQTWQFLS
	DTLR5	VPGENRIANIQDA-IWNSRKIVCLVSRHFLRDGWCL-EAFSYAQGRCLSD
30	DTLR3	EAGVFELEAIVNS-IKRSRKIIFVITHHLLKDPCKRFKVVHAVQQAIEQ
		. * : . * * : : :
35	DTLR1	GSNSLILILLEPIPOYSIPSSYHKLKSLMARRTYLEWPKEKSKRGLFWAN
	DTLR9	GSNNLILILLEPIPQNSIPNKYHKLKALMTQRTYLQWPKEKSKRGLFWA-
	DTLR8	NSDHIILILLEPIPFYCIPTRYHKLKLEALLEKKAYLEWPKDRRKCGLFWAN
	DTLR2	NNDAAIILILLEPIEKKAIPQRFCKLRKIMNTKTYLEWPMDEAQREGFWVN
	DTLR6	KVDVIIIFLEKPFQK---SKFLQLRKRLCGSSVLEWPTNPQAHFYFWQC
	DTLR7	NMDVIIIFILLEPVLQH---SPYLRRLRQICKSSILOWPDNPKAERLFWQT
	DTLR10	-----
40	DTLR4	SRAGIIFIVLQKVEKT-LLRQQVELYRLLSRNTYLEWEDSVLGRHIFWRR
	DTLR5	LNSALIMVVVGSLSQY-QLMKHQSIIRGFVQKQYLRWPEDLQDVGWFLHK
	DTLR3	NLDSIILVFLEEIPDYKLNHALCLRRGMFKSHCILNWPVQKERIGAFRHK
45	DTLR1	LRAAINIKLTEQAKK-----
	DTLR9	-----
	DTLR8	LRAAVNVNVLATREMYELQTFTELNEESRGSTISLMRTDCL
	DTLR2	LRAAIKS-----
	DTLR6	LKNALATDNHVAYSQVFKETV-----
50	DTLR7	LXNVVLTENDSRYNMYVDSIKQY-----
	DTLR10	-----
	DTLR4	LRKALLDGKSWNPEGTVGTGCNWQEATSI-----
	DTLR5	LSQQILKKEKEKKDNNIPLQTVATIS-----
	DTLR3	LQVALGSKNSVH-----
55		

As used herein, the term DNAX Toll like receptor 2 (DTLR2) shall be used to describe a protein comprising a protein or peptide segment having or sharing the amino acid sequence shown in SEQ ID NO: 4, or a substantial fragment thereof. Similarly, with a DTLR3 and SEQ ID NO: 6; DTLR4 and SEQ ID NO: 26; DTLR5 and SEQ ID NO: 10; DTLR6 and SEQ ID NO: 12; DTLR7 and SEQ ID NO: 16 and 18; DTLR8 and SEQ ID NO: 32; DTLR9 and SEQ ID NO: 22; and DTLR10 and SEQ ID NO: 34.

The invention also includes a protein variations of the respective DTLR allele whose sequence is provided, e.g., a mutein agonist or antagonist. Typically, such agonists or antagonists will exhibit less than about 10% sequence differences, and thus will often have between 1- and 11-fold substitutions, e.g., 2-, 3-, 5-, 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphic, of the protein described. Typically, it will bind to its corresponding biological receptor with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall also be used herein to refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein.

This invention also encompasses proteins or peptides having substantial amino acid sequence identity with the amino acid sequence in SEQ ID NO: 4. It will include sequence variants with relatively few substitutions, e.g., preferably less than about 3-5. Similar features apply to the other DTLR sequences provided in SEQ ID NO: 6, 26, 10, 12, 16, 18, 32, 22 and 34.

A substantial polypeptide "fragment", or "segment", is a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14

amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. Sequences of segments of different proteins can be compared to one another over appropriate length stretches.

10 Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches, if necessary, by introducing gaps as required. See, e.g., Needleham, et al., (1970) J. Mol. Biol. 48:443-453; Sankoff, et al., (1983) chapter one in Time Warps, String  
15 Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; each of which is incorporated  
20 herein by reference. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and  
25 phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous proteins or peptides will have from 50-100% homology (if gaps can be introduced), to 60-100% homology (if  
30 conservative substitutions are included) with an amino acid sequence segment of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34. Homology measures will be at least about 70%, generally at least 76%, more generally at  
35 least 81%, often at least 85%, more often at least 88%, typically at least 90%, more typically at least 92%, usually at least 94%, more usually at least 95%,



preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree of homology will vary with the length of the compared segments. Homologous proteins or peptides, such as the allelic variants, will share most biological activities with the embodiments described in SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34. Particularly interesting regions of comparison, at the amino acid or nucleotide levels, correspond to those within each of the blocks 1-10, or intrablock regions, corresponding to those indicated in Figure 2A.

As used herein, the term "biological activity" is used to describe, without limitation, effects on inflammatory responses, innate immunity, and/or morphogenic development by respective ligands. For example, these receptors should, like IL-1 receptors, mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738. The receptors exhibit biological activities much like regulatable enzymes, regulated by ligand binding. However, the enzyme turnover number is more close to an enzyme than a receptor complex. Moreover, the numbers of occupied receptors necessary to induce such enzymatic activity is less than most receptor systems, and may number closer to dozens per cell, in contrast to most receptors which will trigger at numbers in the thousands per cell. The receptors, or portions thereof, may be useful as phosphate labeling enzymes to label general or specific substrates.

The terms ligand, agonist, antagonist, and analog of, e.g., a DTLR, include molecules that modulate the

characteristic cellular responses to Toll ligand like proteins, as well as molecules possessing the more standard structural binding competition features of ligand-receptor interactions, e.g., where the receptor is  
5 a natural receptor or an antibody. The cellular responses likely are mediated through binding of various Toll ligands to cellular receptors related to, but possibly distinct from, the type I or type II IL-1 receptors. See, e.g., Belvin and Anderson (1996) Ann.  
10 Rev. Cell Dev. Biol. 12:393-416; Morisato and Anderson (1995) Ann. Rev. Genetics 29:371-3991 and Hultmark (1994) Nature 367:116-117.

Also, a ligand is a molecule which serves either as a natural ligand to which said receptor, or an analog  
15 thereof, binds, or a molecule which is a functional analog of the natural ligand. The functional analog may be a ligand with structural modifications, or may be a wholly unrelated molecule which has a molecular shape which interacts with the appropriate ligand binding  
20 determinants. The ligands may serve as agonists or antagonists, see, e.g., Goodman, et al. (eds) (1990) Goodman & Gilman's: The Pharmacological Bases of Therapeutics, Pergamon Press, New York.

Rational drug design may also be based upon  
25 structural studies of the molecular shapes of a receptor or antibody and other effectors or ligands. Effectors may be other proteins which mediate other functions in response to ligand binding, or other proteins which normally interact with the receptor. One means for  
30 determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed  
35 description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein

Crystallography, Academic Press, New York, which is hereby incorporated herein by reference.

## II. Activities

5       The Toll like receptor proteins will have a number of different biological activities, e.g., in phosphate metabolism, being added to or removed from specific substrates, typically proteins. Such will generally result in modulation of an inflammatory function, other  
10   innate immunity response, or a morphological effect. The DTLR2, 3, 4, 5, 6, 7, 8, 9, or 10 proteins are homologous to other Toll like receptor proteins, but each have structural differences. For example, a human DTLR2 gene coding sequence probably has about 70% identity with the  
15   nucleotide coding sequence of mouse DTLR2. At the amino acid level, there is also likely to be reasonable identity.

      The biological activities of the DTLRs will be related to addition or removal of phosphate moieties to  
20   substrates, typically in a specific manner, but occasionally in a non specific manner. Substrates may be identified, or conditions for enzymatic activity may be assayed by standard methods, e.g., as described in Hardie, et al. (eds. 1995) The Protein Kinase FactBook  
25   vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature  
30   363:736-738.

## III. Nucleic Acids

      This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely  
35   related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers

isolated or recombinant DNA which encodes such proteins or polypeptides having characteristic sequences of the respective DTLRs, individually or as a group. Typically, the nucleic acid is capable of hybridizing, under  
5 appropriate conditions, with a nucleic acid sequence segment shown in SEQ ID NOs: 3, 5, 25, 9, 11, 15, 17, 31, 21, or 33, but preferably not with a corresponding segment of SEQ ID NO: 1. Said biologically active protein or polypeptide can be a full length protein, or  
10 fragment, and will typically have a segment of amino acid sequence highly homologous to one shown in SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode proteins  
15 having fragments which are equivalent to the DTLR2-10 proteins. The isolated nucleic acids can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene.

20 An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially pure, e.g., separated from other components which naturally accompany a native sequence, such as ribosomes, polymerases, and flanking genomic sequences from the  
25 originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates, which are thereby distinguishable from naturally occurring compositions, and chemically  
30 synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes isolated forms of the molecule, either completely or substantially pure.

An isolated nucleic acid will generally be a  
35 homogeneous composition of molecules, but will, in some embodiments, contain heterogeneity, preferably minor. This heterogeneity is typically found at the polymer ends

or portions not critical to a desired biological function or activity.

A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as found in their natural state. Thus, for example, products made by transforming cells with any unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such a process is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site. Alternatively, the process is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms, e.g., encoding a fusion protein. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. This will include a dimeric repeat. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode equivalent

polypeptides to fragments of DTLR2-10 and fusions of sequences from various different related molecules, e.g., other IL-1 receptor family members.

A "fragment" in a nucleic acid context is a  
5 contiguous segment of at least about 17 nucleotides,  
generally at least 21 nucleotides, more generally at  
least 25 nucleotides, ordinarily at least 30 nucleotides,  
more ordinarily at least 35 nucleotides, often at least  
39 nucleotides, more often at least 45 nucleotides,  
10 typically at least 50 nucleotides, more typically at  
least 55 nucleotides, usually at least 60 nucleotides,  
more usually at least 66 nucleotides, preferably at least  
72 nucleotides, more preferably at least 79 nucleotides,  
and in particularly preferred embodiments will be at  
15 least 85 or more nucleotides. Typically, fragments of  
different genetic sequences can be compared to one  
another over appropriate length stretches, particularly  
defined segments such as the domains described below.

A nucleic acid which codes for a DTLR2-10 will be  
20 particularly useful to identify genes, mRNA, and cDNA  
species which code for itself or closely related  
proteins, as well as DNAs which code for polymorphic,  
allelic, or other genetic variants, e.g., from different  
individuals or related species. Preferred probes for  
25 such screens are those regions of the interleukin which  
are conserved between different polymorphic variants or  
which contain nucleotides which lack specificity, and  
will preferably be full length or nearly so. In other  
situations, polymorphic variant specific sequences will  
30 be more useful.

This invention further covers recombinant nucleic  
acid molecules and fragments having a nucleic acid  
sequence identical to or highly homologous to the  
isolated DNA set forth herein. In particular, the  
35 sequences will often be operably linked to DNA segments  
which control transcription, translation, and DNA

replication. These additional segments typically assist in expression of the desired nucleic acid segment.

Homologous, or highly identical, nucleic acid sequences, when compared to one another or the sequences shown in SEQ ID NO: 3, 5, 25, 9, 11, 15, 17, 31, 21, or 33 exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison or based upon hybridization conditions. Comparative hybridization conditions are described in greater detail below.

Substantial identity in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%, more preferably at least about 96 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides, including, e.g., segments encoding structural domains such as the segments described below. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement, typically using a sequence derived from SEQ ID NO: 3, 5, 25, 9, 11, 15, 17, 31, 21, or 33.

Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) Nuc. Acids Res. 12:203-213, which is incorporated herein by reference. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be

over a stretch of at least about 17 nucleotides,  
generally at least about 20 nucleotides, ordinarily at  
least about 24 nucleotides, usually at least about 28  
nucleotides, typically at least about 32 nucleotides,  
5 more typically at least about 40 nucleotides, preferably  
at least about 50 nucleotides, and more preferably at  
least about 75 to 100 or more nucleotides.

Stringent conditions, in referring to homology in  
the hybridization context, will be stringent combined  
10 conditions of salt, temperature, organic solvents, and  
other parameters typically controlled in hybridization  
reactions. Stringent temperature conditions will usually  
include temperatures in excess of about 30° C, more  
usually in excess of about 37° C, typically in excess of  
15 about 45° C, more typically in excess of about 55° C,  
preferably in excess of about 65° C, and more preferably  
in excess of about 70° C. Stringent salt conditions will  
ordinarily be less than about 500 mM, usually less than  
about 400 mM, more usually less than about 300 mM,  
20 typically less than about 200 mM, preferably less than  
about 100 mM, and more preferably less than about 80 mM,  
even down to less than about 20 mM. However, the  
combination of parameters is much more important than the  
measure of any single parameter. See, e.g., Wetmur and  
25 Davidson (1968) J. Mol. Biol. 31:349-370, which is hereby  
incorporated herein by reference.

Alternatively, for sequence comparison, typically  
one sequence acts as a reference sequence, to which test  
sequences are compared. When using a sequence comparison  
30 algorithm, test and reference sequences are input into a  
computer, subsequence coordinates are designated, if  
necessary, and sequence algorithm program parameters are  
designated. The sequence comparison algorithm then  
calculates the percent sequence identity for the test  
35 sequence(s) relative to the reference sequence, based on  
the designated program parameters.



Optical alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2:482, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally Ausubel et al., supra).

One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments to show relationship and percent sequence identity. It also plots a tree or dendrogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng and Doolittle (1987) J. Mol. Evol. 35:351-360. The method used is similar to the method described by Higgins and Sharp (1989) CABIOS 5:151-153. The program can align up to 300 sequences, each of a maximum length of 5,000 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the next most related sequence or cluster of aligned sequences. Two clusters of sequences are aligned by a simple extension of the pairwise alignment of two individual sequences. The final alignment is achieved by a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence comparison and by designating the program parameters. For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following

parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps.

Another example of algorithm that is suitable for determining percent sequence identity and sequence  
5 similarity is the BLAST algorithm, which is described Altschul, et al. (1990) J. Mol. Biol. 215:403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm  
10 involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is  
15 referred to as the neighborhood word score threshold (Altschul, et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as  
20 far as the cumulative alignment score can be increased. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the  
25 accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a wordlength (W) of 11, the  
30 BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) Proc. Nat'l Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

In addition to calculating percent sequence  
35 identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) Proc. Nat'l Acad. Sci.

USA 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability ( $P(N)$ ), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

A further indication that two nucleic acid sequences of polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, e.g., where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

The isolated DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode this protein or its derivatives. These modified sequences can be used to produce mutant proteins (muteins) or to enhance the expression of variant species. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant DTLR-like derivatives include predetermined or site-specific mutations of the protein or its fragments, including silent mutations using genetic code degeneracy. "Mutant DTLR" as used herein encompasses a polypeptide otherwise falling within the homology definition of the DTLR as set

forth above, but having an amino acid sequence which differs from that of other DTLR-like proteins as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant DTLR" encompasses a protein having substantial homology with a protein of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34, and typically shares most of the biological activities or effects of the forms disclosed herein.

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian DTLR mutagenesis can be achieved by making amino acid insertions or deletions in the gene, coupled with expression. Substitutions, deletions, insertions, or any combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy-terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian DTLR mutants can then be screened for the desired activity. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al. (1987 and periodic Supplements).

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polymerase chain reaction (PCR) techniques can often be applied in mutagenesis. Alternatively, mutagenesis primers are commonly used methods for generating defined mutations at predetermined sites. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (1995; eds.) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY.

10 IV. Proteins, Peptides

As described above, the present invention encompasses primate DTLR2-10, e.g., whose sequences are disclosed in SEQ ID NOS: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34, and described above. Allelic and other variants are also contemplated, including, e.g., fusion proteins combining portions of such sequences with others, including epitope tags and functional domains.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these rodent proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of a DTLR with an IL-1 receptor is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting properties, e.g., sequence or antigenicity, derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences.

30 In addition, new constructs may be made from combining similar functional or structural domains from other related proteins, e.g., IL-1 receptors or other DTLRs, including species variants. For example, ligand-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992,

each of which is incorporated herein by reference. Thus, new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of receptor-binding specificities. For example, the ligand  
5 binding domains from other related receptor molecules may be added or substituted for other domains of this or related proteins. The resulting protein will often have hybrid function and properties. For example, a fusion protein may include a targetting domain which may serve  
10 to provide sequestering of the fusion protein to a particular subcellular organelle.

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank, c/o IntelliGenetics, Mountain View, CA; and BCG,  
15 University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated herein by reference.

The present invention particularly provides muteins which bind Toll ligands, and/or which are affected in  
20 signal transduction. Structural alignment of human DTLR1-10 with other members of the IL-1 family show conserved features/residues. See, e.g., Figure 3A. Alignment of the human DTLR sequences with other members of the IL-1 family indicates various structural and  
25 functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.

30 The IL-1 $\alpha$  and IL-1 $\beta$  ligands bind an IL-1 receptor type I as the primary receptor and this complex then forms a high affinity receptor complex with the IL-1 receptor type III. Such receptor subunits are probably shared with the new IL-1 family members.

35 Similar variations in other species counterparts of DTLR2-10 sequences, e.g., in the corresponding regions, should provide similar interactions with ligand or

substrate. Substitutions with either mouse sequences or human sequences are particularly preferred. Conversely, conservative substitutions away from the ligand binding interaction regions will probably preserve most signaling activities.

"Derivatives" of the primate DTLR2-10 include amino acid sequence mutants, glycosylation variants, metabolic derivatives and covalent or aggregative conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in the DTLR amino acid side chains or at the N- or C- termini, e.g., by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties including C3 to C18-normal alkyl, thereby forming alkanoyl aroyl species.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the receptors or fragments thereof with other proteins of polypeptides. These derivatives can be synthesized in

recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between the receptors and other homologous or heterologous proteins are also provided. Homologous polypeptides may be fusions between different receptors, resulting in, for instance, a hybrid protein exhibiting binding specificity for multiple different Toll ligands, or a receptor which may have broadened or weakened specificity of substrate effect. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a receptor, e.g., a ligand-binding segment, so that the presence or location of a desired ligand may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609, which is hereby incorporated herein by reference. Other gene fusion partners include glutathione-S-transferase (GST), bacterial  $\beta$ -galactosidase, trpE, Protein A,  $\beta$ -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation,



sulfonation, biotinylation, or the addition or removal of other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or  
5 serve as purification targets, e.g., affinity ligands.

Fusion proteins will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide methods. Techniques for nucleic acid manipulation and expression are described generally, for  
10 example, in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory, and Ausubel, et al. (eds. 1987 and periodic supplements) Current Protocols in Molecular Biology,  
15 Greene/Wiley, New York, which are each incorporated herein by reference. Techniques for synthesis of polypeptides are described, for example, in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 232: 341-347; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL  
20 Press, Oxford; each of which is incorporated herein by reference. See also Dawson, et al. (1994) Science 266:776-779 for methods to make larger polypeptides.

This invention also contemplates the use of derivatives of a DTLR2-10 other than variations in amino  
25 acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for  
30 example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, a Toll  
35 ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed onto

polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of a DTLR receptor, antibodies, or other similar molecules. The ligand can also be labeled with a detectable group, for example radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

A DTLR of this invention can be used as an immunogen for the production of antisera or antibodies specific, e.g., capable of distinguishing between other IL-1 receptor family members, for the DTLR or various fragments thereof. The purified DTLR can be used to screen monoclonal antibodies or antigen-binding fragments prepared by immunization with various forms of impure preparations containing the protein. In particular, the term "antibodies" also encompasses antigen binding fragments of natural antibodies, e.g., Fab, Fab2, Fv, etc. The purified DTLR can also be used as a reagent to detect antibodies generated in response to the presence of elevated levels of expression, or immunological disorders which lead to antibody production to the endogenous receptor. Additionally, DTLR fragments may also serve as immunogens to produce the antibodies of the present invention, as described immediately below. For example, this invention contemplates antibodies having binding affinity to or being raised against the amino acid sequences shown in SEQ ID NOS: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34, fragments thereof, or various homologous peptides. In particular, this invention contemplates antibodies having binding affinity to, or having been raised against, specific fragments which are predicted to be, or actually are, exposed at the exterior protein surface of the native DTLR.

The blocking of physiological response to the receptor ligands may result from the inhibition of binding of the ligand to the receptor, likely through competitive inhibition. Thus, in vitro assays of the

present invention will often use antibodies or antigen binding segments of these antibodies, or fragments attached to solid phase substrates. These assays will also allow for the diagnostic determination of the effects of either ligand binding region mutations and modifications, or other mutations and modifications, e.g., which affect signaling or enzymatic function.

This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to the receptor or fragments compete with a test compound for binding to a ligand or other antibody. In this manner, the neutralizing antibodies or fragments can be used to detect the presence of a polypeptide which shares one or more binding sites to a receptor and can also be used to occupy binding sites on a receptor that might otherwise bind a ligand.

#### V. Making Nucleic Acids and Protein

DNA which encodes the protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Natural sequences can be isolated using standard methods and the sequences provided herein. Other species counterparts can be identified by hybridization techniques, or by various PCR techniques, combined with or by searching in sequence databases, e.g., GenBank.

This DNA can be expressed in a wide variety of host cells for the synthesis of a full-length receptor or fragments which can in turn, for example, be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified ligand binding or kinase/phosphatase domains; and for structure/function studies. Variants or fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These

molecules can be substantially free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The protein, or portions thereof, may be expressed as fusions with other proteins.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired receptor gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

The vectors of this invention include those which contain DNA which encodes a protein, as described, or a fragment thereof encoding a biologically active equivalent polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNA coding for such a protein in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNA coding for the receptor is inserted into the vector such

that growth of the host containing the vector expresses the cDNA in question. Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of  
5 copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication  
10 origin that is recognized by the host cell. It is also possible to use vectors that cause integration of the protein encoding portion or its fragments into the host DNA by recombination.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other  
15 vehicles which enable the integration of DNA fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector but  
20 all other forms of vectors which serve an equivalent function and which are, or become, known in the art are suitable for use herein. See, e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory  
25 Manual, Elsevier, N.Y., and Rodriguez, et al. (eds) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Butterworth, Boston, 1988, which are incorporated herein by reference.

Transformed cells are cells, preferably mammalian, that have been transformed or transfected with receptor  
30 vectors constructed using recombinant DNA techniques. Transformed host cells usually express the desired protein or its fragments, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to  
35 express the subject protein. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the receptor to accumulate in the

cell membrane. The protein can be recovered, either from the culture or, in certain instances, from the culture medium.

For purposes of this invention, nucleic sequences  
5 are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in  
10 secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably  
15 linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression.

Suitable host cells include prokaryotes, lower  
20 eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts, e.g., S. cerevisiae and Pichia, and species of the genus Dictyostelium. Higher eukaryotes include established  
25 tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used  
30 herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be used to express the receptor or its fragments include, but are  
35 not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters

(pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Vectors: A Survey of Molecular Cloning Vectors and Their  
5 Uses, (eds. Rodriguez and Denhardt), Butterworth, Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with DTLR sequence containing vectors.  
10 For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically  
15 consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the receptor or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors  
20 for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothionine promoter. Suitable vectors include derivatives of the  
25 following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YEp-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

30 Higher eukaryotic tissue culture cells are normally the preferred host cells for expression of the functionally active interleukin protein. In principle, any higher eukaryotic tissue culture cell line is workable, e.g., insect baculovirus expression systems,  
35 whether from an invertebrate or vertebrate source. However, mammalian cells are preferred. Transformation or transfection and propagation of such cells has become

a routine procedure. Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines.

5 Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a  
10 selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of  
15 suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo PolyA, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

For secreted proteins, an open reading frame usually  
20 encodes a polypeptide that consists of a mature or secreted product covalently linked at its N-terminus to a signal peptide. The signal peptide is cleaved prior to secretion of the mature, or active, polypeptide. The cleavage site can be predicted with a high degree of  
25 accuracy from empirical rules, e.g., von-Heijne (1986) Nucleic Acids Research 14:4683-4690, and the precise amino acid composition of the signal peptide does not appear to be critical to its function, e.g., Randall, et al. (1989) Science 243:1156-1159; Kaiser et al. (1987)  
30 Science 235:312-317.

It will often be desired to express these polypeptides in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression  
35 system. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a



heterologous expression system. For example, the receptor gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. Using this approach, certain mammalian glycosylation patterns will be achievable in prokaryote or other cells.

The source of DTLR can be a eukaryotic or prokaryotic host expressing recombinant DTLR, such as is described above. The source can also be a cell line such as mouse Swiss 3T3 fibroblasts, but other mammalian cell lines are also contemplated by this invention, with the preferred cell line being from the human species.

Now that the sequences are known, the primate DTLRs, fragments, or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York; all of each which are incorporated herein by reference. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (e.g., p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes. Similar techniques can be used with partial DTLR sequences.

The DTLR proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to

the terminal amino acid. Amino groups that are not being used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the  
5 C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl  
10 resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonylhydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl  
15 group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is  
20 generally described by Merrifield, et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means  
25 of peptide separation, for example, by extraction, precipitation, electrophoresis, various forms of chromatography, and the like. The receptors of this invention can be obtained in varying degrees of purity depending upon desired uses. Purification can be  
30 accomplished by use of the protein purification techniques disclosed herein, see below, or by the use of the antibodies herein described in methods of immunoabsorbant affinity chromatography. This  
immunoabsorbant affinity chromatography is carried out by  
35 first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate cells, lysates of other cells expressing

the receptor, or lysates or supernatants of cells producing the protein as a result of DNA techniques, see below.

Generally, the purified protein will be at least  
5 about 40% pure, ordinarily at least about 50% pure, usually at least about 60% pure, typically at least about 70% pure, more typically at least about 80% pure, preferable at least about 90% pure and more preferably at least about 95% pure, and in particular embodiments, 97%-  
10 99% or more. Purity will usually be on a weight basis, but can also be on a molar basis. Different assays will be applied as appropriate.

#### VI. Antibodies

15 Antibodies can be raised to the various mammalian, e.g., primate DTLR proteins and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize  
20 epitopes which are only present in the native conformations. Denatured antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which would be useful as agonists or antagonists of a natural receptor or an  
25 antibody.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of the protein can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins.  
30 Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective protein, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a  $K_D$  of about  
35 1 mM, more usually at least about 300  $\mu$ M, typically at least about 100  $\mu$ M, more typically at least about 30  $\mu$ M,

preferably at least about 10  $\mu\text{M}$ , and more preferably at least about 3  $\mu\text{M}$  or better.

The antibodies, including antigen binding fragments, of this invention can have significant diagnostic or therapeutic value. They can be potent antagonists that bind to the receptor and inhibit binding to ligand or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate. They also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides to bind producing cells, or cells localized to the source of the interleukin. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker.

The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they might bind to the receptor without inhibiting ligand or substrate binding. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in detecting or quantifying ligand. They may be used as reagents for Western blot analysis, or for immunoprecipitation or immunopurification of the respective protein.

Protein fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. Mammalian DTLR and its fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York; each of which are incorporated herein by reference, for descriptions of methods of preparing polyclonal antisera. A typical

method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma globulin is isolated.

5        In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds) Basic and  
10 Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York;  
15 and particularly in Kohler and Milstein (1975) in Nature 256: 495-497, which discusses one method of generating monoclonal antibodies. Each of these references is incorporated herein by reference. Summarized briefly, this method involves injecting an animal with an  
20 immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones,  
25 each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic  
30 substance.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989)  
35 "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-

546, each of which is hereby incorporated herein by reference. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies.

5 Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific

10 and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos.

15 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant or chimeric immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; or made in transgenic mice, see Mendez, et al. (1997) Nature Genetics 15:146-156. These references

20 are incorporated herein by reference.

The antibodies of this invention can also be used for affinity chromatography in isolating the DTLRs. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose,

25 Sephadex, or the like, where a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be released. The protein may be used to purify antibody.

30 The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

35 Antibodies raised against a DTLR will also be used to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological

conditions related to expression of the protein or cells which express the protein. They also will be useful as agonists or antagonists of the ligand, which may be competitive inhibitors or substitutes for naturally occurring ligands.

A DTLR protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34, is typically determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34. This antiserum is selected to have low crossreactivity against other IL-1R family members, e.g., DTLR1, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay.

In order to produce antisera for use in an immunoassay, the protein of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34, or a combination thereof, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as balb/c, is immunized with the selected protein, typically using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, supra). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used as an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of  $10^4$  or greater are selected and tested for their cross reactivity against other IL-1R family members, e.g., mouse DTLRs or human DTLR1, using a competitive binding

immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably at least two DTLR family members are used in this determination in conjunction with either or some of the human DTLR2-10.

- 5 These IL-1R family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For  
10 example, the proteins of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34, or various fragments thereof, can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins  
15 to compete with the binding of the antisera to the immobilized protein is compared to the protein of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 and/or 34. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera  
20 with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorbtion with the above-listed proteins.

- 25 The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., the IL-1R like protein of SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 and/or 34). In order to make this  
30 comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount  
35 of the protein of the selected protein or proteins that is required, then the second protein is said to



specifically bind to an antibody generated to the immunogen.

It is understood that these DTLR proteins are members of a family of homologous proteins that comprise at least 10 so far identified genes. For a particular gene product, such as the DTLR2-10, the term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are allelic, non-allelic or species variants. It also understood that the terms include nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding the respective proteins, or by substituting new amino acids, or adding new amino acids. Such minor alterations must substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring IL-1R related protein, for example, the DTLR proteins shown in SEQ ID NO: 4, 6, 26, 10, 12, 16, 18, 32, 22 or 34. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring the appropriate effect upon lymphocytes. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for the IL-1R family as a whole. By aligning a protein optimally with the protein of DTLR2-10 and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the protein compositions of the invention.

#### VII. Kits and quantitation

Both naturally occurring and recombinant forms of the IL-1R like molecules of this invention are particularly useful in kits and assay methods. For example, these methods would also be applied to screening

for binding activity, e.g., ligands for these proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds per year. See, e.g., a BIOMEK  
5 automated workstation, Beckman Instruments, Palo Alto, California, and Fodor, et al. (1991) Science 251:767-773, which is incorporated herein by reference. The latter describes means for testing binding by a plurality of defined polymers synthesized on a solid substrate. The  
10 development of suitable assays to screen for a ligand or agonist/antagonist homologous proteins can be greatly facilitated by the availability of large amounts of purified, soluble DTLRs in an active state such as is provided by this invention.

15 Purified DTLR can be coated directly onto plates for use in the aforementioned ligand screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture antibodies to immobilize the respective receptor on the solid phase, useful, e.g., in  
20 diagnostic uses.

This invention also contemplates use of DTLR2-10, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of the protein or its ligand.

25 Alternatively, or additionally, antibodies against the molecules may be incorporated into the kits and methods. Typically the kit will have a compartment containing either a defined DTLR peptide or gene segment or a reagent which recognizes one or the other. Typically,  
30 recognition reagents, in the case of peptide, would be a receptor or antibody, or in the case of a gene segment, would usually be a hybridization probe.

A preferred kit for determining the concentration of, e.g., DTLR4, a sample would typically comprise a  
35 labeled compound, e.g., ligand or antibody, having known binding affinity for DTLR4, a source of DTLR4 (naturally occurring or recombinant) as a positive control, and a

means for separating the bound from free labeled compound, for example a solid phase for immobilizing the DTLR4 in the test sample. Compartments containing reagents, and instructions, will normally be provided.

5       Antibodies, including antigen binding fragments, specific for mammalian DTLR or a peptide fragment, or receptor fragments are useful in diagnostic applications to detect the presence of elevated levels of ligand and/or its fragments. Diagnostic assays may be  
10       homogeneous (without a separation step between free reagent and antibody-antigen complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA),  
15       enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA) and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to DTLR4 or to a particular  
20       fragment thereof. These assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH., and Coligan (Ed.) (1991) and periodic supplements, Current Protocols In Immunology Greene/Wiley, New York.

25       Anti-idiotypic antibodies may have similar use to serve as agonists or antagonists of DTLR4. These should be useful as therapeutic reagents under appropriate circumstances.

30       Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody, or labeled ligand is provided. This is usually in conjunction with other  
35       additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also

contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent, and will contain instructions for proper use and disposal of reagents. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium having appropriate concentrations for performing the assay.

The aforementioned constituents of the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In any of these assays, a test compound, DTLR, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as  $^{125}\text{I}$ , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Both of the patents are incorporated herein by reference. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free ligand, or alternatively the bound from the free test compound. The DTLR can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the receptor to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of antibody/antigen complex by any of several methods including those utilizing, e.g.,

an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in  
5 Rattle, et al. (1984) Clin. Chem. 30(9):1457-1461, and the double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678, each of which is incorporated herein by reference.

The methods for linking protein or fragments to  
10 various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of  
15 thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves  
20 use of oligonucleotide or polynucleotide sequences taken from the sequence of a DTLR. These sequences can be used as probes for detecting levels of the respective DTLR in patients suspected of having an immunological disorder. The preparation of both RNA and DNA nucleotide sequences,  
25 the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and  
30 the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly radionuclides, particularly  $^{32}\text{P}$ . However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a  
35 polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides,

fluorescers, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies  
5 in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out in  
10 any conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes  
amplification techniques such as polymerase chain  
15 reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers.  
20 Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

#### VIII. Therapeutic Utility

25 This invention provides reagents with significant therapeutic value. The DTLRs (naturally occurring or recombinant), fragments thereof, mutein receptors, and antibodies, along with compounds identified as having binding affinity to the receptors or antibodies, should  
30 be useful in the treatment of conditions exhibiting abnormal expression of the receptors of their ligands. Such abnormality will typically be manifested by immunological disorders. Additionally, this invention should provide therapeutic value in various diseases or  
35 disorders associated with abnormal expression or abnormal triggering of response to the ligand. The Toll ligands have been suggested to be involved in morphologic

development, e.g., dorso-ventral polarity determination, and immune responses, particularly the primitive innate responses. See, e.g., Sun, et al. (1991) Eur. J. Biochem. 196:247-254; Hultmark (1994) Nature 367:116-117.

5       Recombinant DTLRs, muteins, agonist or antagonist antibodies thereto, or antibodies can be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active ingredients, e.g., in conventional pharmaceutically  
10 acceptable carriers or diluents, along with physiologically innocuous stabilizers and excipients. These combinations can be sterile, e.g., filtered, and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations.  
15 This invention also contemplates use of antibodies or binding fragments thereof which are not complement binding.

      Ligand screening using DTLR or fragments thereof can be performed to identify molecules having binding  
20 affinity to the receptors. Subsequent biological assays can then be utilized to determine if a putative ligand can provide competitive binding, which can block intrinsic stimulating activity. Receptor fragments can be used as a blocker or antagonist in that it blocks the  
25 activity of ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of ligand, e.g., inducing signaling. This invention further contemplates the therapeutic use of antibodies to  
30 DTLRs as antagonists.

      The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medicants  
35 administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts

useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, (current edition), Mack Publishing Co., Easton, Penn.; each of which is hereby incorporated herein by reference. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Because of the likely high affinity binding, or turnover numbers, between a putative ligand and its receptors, low dosages of these reagents would be initially expected to be effective. And the signaling pathway suggests extremely low amounts of ligand may have effect. Thus, dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10  $\mu$ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or slow release apparatus will often be utilized for continuous administration.

DTLRs, fragments thereof, and antibodies or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in any conventional dosage formulation. While it is possible for the active



ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences (current edition), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other therapeutic agents, particularly agonists or antagonists of other IL-1 family members.

#### IX. Ligands

The description of the Toll receptors herein provide means to identify ligands, as described above. Such ligand should bind specifically to the respective receptor with reasonably high affinity. Various constructs are made available which allow either labeling of the receptor to detect its ligand. For example, directly labeling DTLR, fusing onto it markers for secondary labeling, e.g., FLAG or other epitope tags, etc., will allow detection of receptor. This can be histological, as an affinity method for biochemical

purification, or labeling or selection in an expression cloning approach. A two-hybrid selection system may also be applied making appropriate constructs with the available DTLR sequences. See, e.g., Fields and Song  
5 (1989) Nature 340:245-246.

Generally, descriptions of DTLRs will be analogously applicable to individual specific embodiments directed to DTLR2, DTLR3, DTLR4, DTLR5, DTLR6, DTLR7, DTLR8, DTLR9, and/or DTLR10 reagents and compositions.

10 The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the inventions to the specific embodiments.

15

#### EXAMPLES

##### I. General Methods

Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor  
20 Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Methods for  
25 protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Coligan, et al. (ed. 1996) and periodic supplements, Current Protocols In Protein Science Greene/Wiley, New York; Deutscher (1990) "Guide to Protein Purification" in Methods in Enzymology, vol. 182,  
30 and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA.  
35

Combination with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) OIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

Standard immunological techniques and assays are described, e.g., in Hertenberg, et al. (eds. 1996) Weir's Handbook of Experimental Immunology vols. 1-4, Blackwell Science; Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY; and Methods in Enzymology volumes. 70, 73, 74, 84, 92, 93, 108, 116, 121, 132, 150, 162, and 163.

Assays for vascular biological activities are well known in the art. They will cover angiogenic and angiostatic activities in tumor, or other tissues, e.g., arterial smooth muscle proliferation (see, e.g., Koyoma, et al. (1996) Cell 87:1069-1078), monocyte adhesion to vascular epithelium (see McEvoy, et al. (1997) J. Exp. Med. 185:2069-2077), etc. See also Ross (1993) Nature 362:801-809; Reikter and Gordon (1995) Am. J. Pathol. 147:668-677; Thyberg, et al. (1990) Atherosclerosis 10:966-990; and Gumbiner (1996) Cell 84:345-357.

Assays for neural cell biological activities are described, e.g., in Wouterlood (ed. 1995) Neuroscience Protocols modules 10, Elsevier; Methods in Neurosciences Academic Press; and Neuromethods Humana Press, Totowa, NJ. Methodology of developmental systems is described, e.g., in Meisami (ed.) Handbook of Human Growth and Developmental Biology CRC Press; and Chrispeels (ed.) Molecular Techniques and Approaches in Developmental Biology Interscience.

Computer sequence analysis is performed, e.g., using available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence databases were also used, e.g., from GenBank, NCBI, EMBO, and others.

Many techniques applicable to IL-10 receptors may be applied to DTLRs, as described, e.g., in USSN 08/110,683 (IL-10 receptor), which is incorporated herein by reference for all purposes.

## II. Novel Family of Human Receptors

Abbreviations: DTLR, Toll-like receptor; IL-1R, interleukin-1 receptor; TH, Toll homology; LRR, leucine-rich repeat; EST, expressed sequence tag; STS, sequence tagged site; FISH, fluorescence in situ hybridization.

The discovery of sequence homology between the cytoplasmic domains of *Drosophila* Toll and human interleukin-1 (IL-1) receptors has sown the conviction that both molecules trigger related signaling pathways tied to the nuclear translocation of Rel-type transcription factors. This conserved signaling scheme governs an evolutionarily ancient immune response in both insects and vertebrates. We report the molecular cloning of a novel class of putative human receptors with a protein architecture that is closely similar to *Drosophila* Toll in both intra- and extra-cellular segments. Five human Toll-like receptors, designated DTLRs 1-5, are likely the direct homologs of the fly molecule, and as such could constitute an important and unrecognized component of innate immunity in humans; intriguingly, the evolutionary retention of DTLRs in vertebrates may indicate another role, akin to Toll in the dorso-ventralization of the *Drosophila* embryo, as regulators of early morphogenetic patterning. Multiple tissue mRNA blots indicate markedly different patterns of

expression for the human DTLRs. Using fluorescence in situ hybridization and Sequence-Tagged Site database analyses, we also show that the cognate DTLR genes reside on chromosomes 4 (DTLRs 1, 2, and 3), 9 (DTLR4), and 1  
5 (DTLR5). Structure prediction of the aligned Toll-homology (TH) domains from varied insect and human DTLRs, vertebrate IL-1 receptors, and MyD88 factors, and plant disease resistance proteins, recognizes a parallel  $\beta/\alpha$  fold with an acidic active site; a similar structure  
10 notably recurs in a class of response regulators broadly involved in transducing sensory information in bacteria.

The seeds of the morphogenetic gulf that so dramatically separates flies from humans are planted in  
15 familiar embryonic shapes and patterns, but give rise to very different cell complexities. DeRobertis and Sasai (1996) Nature 380:37-40; and Arendt and Nübler-Jung (1997) Mech. Develop. 61:7-21. This divergence of developmental plans between insects and vertebrates is  
20 choreographed by remarkably similar signaling pathways, underscoring a greater conservation of protein networks and biochemical mechanisms from unequal gene repertoires. Miklos and Rubin (1996) Cell 86:521-529; and Chothia (1994) Develop. 1994 Suppl., 27-33. A powerful way to  
25 chart the evolutionary design of these regulatory pathways is by inferring their likely molecular components (and biological functions) through interspecies comparisons of protein sequences and structures. Miklos and Rubin (1996) Cell 86:521-529;  
30 Chothia (1994) Develop. 1994 Suppl., 27-33 (3-5); and Banfi, et al. (1996) Nature Genet. 13:167-174.

A universally critical step in embryonic development is the specification of body axes, either born from innate asymmetries or triggered by external cues.  
35 DeRobertis and Sasai (1996) Nature 380:37-40; and Arendt and Nübler-Jung (1997) Mech. Develop. 61:7-21. As a model system, particular attention has been focused on

the phylogenetic basis and cellular mechanisms of dorsoventral polarization . DeRobertis and Sasai (1996) Nature 380:37-40; and Arendt and Nübler-Jung (1997) Mech. Develop. 61:7-21. A prototype molecular strategy for  
5 this transformation has emerged from the Drosophila embryo, where the sequential action of a small number of genes results in a ventralizing gradient of the transcription factor Dorsal. St. Johnston and Nüsslein-Volhard (1992) Cell 68:201-219; and Morisato and Anderson  
10 (1995) Ann. Rev. Genet. 29:371-399.

This signaling pathway centers on Toll, a transmembrane receptor that transduces the binding of a maternally-secreted ventral factor, Spätzle, into the cytoplasmic engagement of Tube, an accessory molecule,  
15 and the activation of Pelle, a Ser/Thr kinase that catalyzes the dissociation of Dorsal from the inhibitor Cactus and allows migration of Dorsal to ventral nuclei (Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399; and Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416. The Toll pathway also  
20 controls the induction of potent antimicrobial factors in the adult fly (Lemaitre, et al. (1996) Cell 86:973-983); this role in Drosophila immune defense strengthens mechanistic parallels to IL-1 pathways that govern a host  
25 of immune and inflammatory responses in vertebrates. Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Wasserman (1993) Molec. Biol. Cell 4:767-771. A Toll-related cytoplasmic domain in IL-1 receptors directs the binding of a Pelle-like kinase, IRAK, and the  
30 activation of a latent NF- $\kappa$ B/I- $\kappa$ B complex that mirrors the embrace of Dorsal and Cactus. Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Wasserman (1993) Molec. Biol. Cell 4:767-771.

We describe the cloning and molecular  
35 characterization of four new Toll-like molecules in humans, designated DTLRs 2-5 (following Chiang & Beachy (1994) Mech. Develop. 47:225-239), that reveal a receptor

family more closely tied to *Drosophila* Toll homologs than to vertebrate IL-1 receptors. The DTLR sequences are derived from human ESTs; these partial cDNAs were used to draw complete expression profiles in human tissues for the five DTLRs, map the chromosomal locations of cognate genes, and narrow the choice of cDNA libraries for full-length cDNA retrievals. Spurred by other efforts (Banfi, et al. (1996) Nature Genet. 13:167-174; and Wang, et al. (1996) J. Biol. Chem. 271:4468-4476), we are assembling, by structural conservation and molecular parsimony, a biological system in humans that is the counterpart of a compelling regulatory scheme in *Drosophila*. In addition, a biochemical mechanism driving Toll signaling is suggested by the proposed tertiary fold of the Toll-homology (TH) domain, a core module shared by DTLRs, a broad family of IL-1 receptors, mammalian MyD88 factors and plant disease resistance proteins. Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783; and Hardiman, et al. (1996) Oncogene 13:2467-2475. We propose that a signaling route coupling morphogenesis and primitive immunity in insects, plants, and animals (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Wilson, et al. (1997) Curr. Biol. 7:175-178) may have roots in bacterial two-component pathways.

25

#### Computational Analysis.

Human sequences related to insect DTLRs were identified from the EST database (dbEST) at the National Center for Biotechnology Information (NCBI) using the BLAST server (Altschul, et al. (1994) Nature Genet. 6:119-129). More sensitive pattern- and profile-based methods (Bork and Gibson (1996) Meth. Enzymol. 266:162-184) were used to isolate the signaling domains of the DTLR family that are shared with vertebrate and plant proteins present in nonredundant databases. The progressive alignment of DTLR intra- or extracellular domain sequences was carried out by ClustalW (Thompson,

et al. (1994) Nucleic Acids Res. 22:4673-4680); this program also calculated the branching order of aligned sequences by the Neighbor-Joining algorithm (5000 bootstrap replications provided confidence values for the tree groupings).

Conserved alignment patterns, discerned at several degrees of stringency, were drawn by the Consensus program (internet URL <http://www.bork.embl-heidelberg.de/Alignment/consensus.html>). The PRINTS library of protein fingerprints (<http://www.biochem.ucl.ac.uk/bsm/dbbrowser/PRINTS/PRINTS.html>) (Attwood, et al. (1997) Nucleic Acids Res. 25:212-217) reliably identified the myriad leucine-rich repeats (LRRs) present in the extracellular segments of DTLRs with a compound motif (PRINTS code Leurichrpt) that flexibly matches N- and C-terminal features of divergent LRRs. Two prediction algorithms whose three-state accuracy is above 72% were used to derive a consensus secondary structure for the intracellular domain alignment, as a bridge to fold recognition efforts (Fischer, et al. (1996) FASEB J. 10:126-136). Both the neural network program PHD (Rost and Sander (1994) Proteins 19:55-72) and the statistical prediction method DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310) have internet servers (URLs [http://www.embl-heidelberg.de/predictprotein/phd\\_pred.html](http://www.embl-heidelberg.de/predictprotein/phd_pred.html) and [http://bonsai.lif.icnet.uk/bmm/dsc/dsc\\_read\\_align.html](http://bonsai.lif.icnet.uk/bmm/dsc/dsc_read_align.html), respectively). The intracellular region encodes the THD region discussed, e.g., in Hardiman, et al. (1996) Oncogene 13:2467-2475; and Rock, et al. (1998) Proc. Nat'l Acad. Sci. USA 95:588-593, each of which is incorporated herein by reference. This domain is very important in the mechanism of signaling by the receptors, which transfers a phosphate group to a substrate.

Cloning of full-length human DTLR cDNAs.



PCR primers derived from the Toll-like Humrsc786 sequence (Genbank accession code D13637) (Nomura, et al. (1994) DNA Res 1:27-35) were used to probe a human erythroleukemic, TF-1 cell line-derived cDNA library (Kitamura, et al. (1989) Blood 73:375-380) to yield the DTLR1 cDNA sequence. The remaining DTLR sequences were flagged from dbEST, and the relevant EST clones obtained from the I.M.A.G.E. consortium (Lennon, et al. (1996) Genomics 33:151-152) via Research Genetics (Huntsville, AL): CloneID#'s 80633 and 117262 (DTLR2), 144675 (DTLR3), 202057 (DTLR4) and 277229 (DTLR5). Full length cDNAs for human DTLRs 2-4 were cloned by DNA hybridization screening of  $\lambda$ gt10 phage, human adult lung, placenta, and fetal liver 5'-Stretch Plus cDNA libraries (Clontech), respectively; the DTLR5 sequence is derived from a human multiple-sclerosis plaque EST. All positive clones were sequenced and aligned to identify individual DTLR ORFs: DTLR1 (2366 bp clone, 786 aa ORF), DTLR2 (2600 bp, 784 aa), DTLR3 (3029 bp, 904 aa), DTLR4 (3811 bp, 879 aa) and DTLR5 (1275 bp, 370 aa). Probes for DTLR3 and DTLR4 hybridizations were generated by PCR using human placenta (Stratagene) and adult liver (Clontech) cDNA libraries as templates, respectively; primer pairs were derived from the respective EST sequences. PCR reactions were conducted using *T. aquaticus* Taqplus DNA polymerase (Stratagene) under the following conditions: 1 x (94° C, 2 min) 30 x (55° C, 20 sec; 72° C 30 sec; 94° C 20 sec), 1 x (72° C, 8 min). For DTLR2 full-length cDNA screening, a 900 bp fragment generated by EcoRI/XbaI digestion of the first EST clone (ID# 80633) was used as a probe.

mRNA blots and chromosomal localization.

Human multiple tissue (Cat# 1, 2) and cancer cell line blots (Cat# 7757-1), containing approximately 2  $\mu$ g of poly(A)<sup>+</sup> RNA per lane, were purchased from Clontech (Palo Alto, CA). For DTLRs 1-4, the isolated full-length

cDNAs served as probes, for DTLR5 the EST clone (ID #277229) plasmid insert was used. Briefly, the probes were radiolabeled with [ $\alpha$ - $^{32}$ P] dATP using the Amersham Rediprime random primer labeling kit (RPN1633).

- 5 Prehybridization and hybridizations were performed at 65° C in 0.5 M Na<sub>2</sub>HPO<sub>4</sub>, 7% SDS, 0.5 M EDTA (pH 8.0). All stringency washes were conducted at 65° C with two initial washes in 2 x SSC, 0.1% SDS for 40 min followed by a subsequent wash in 0.1 x SSC, 0.1% SDS for 20 min.
- 10 Membranes were then exposed at -70° C to X-Ray film (Kodak) in the presence of intensifying screens. More detailed studies by cDNA library Southern (14) were performed with selected human DTLR clones to examine their expression in hemopoietic cell subsets.
- 15 Human chromosomal mapping was conducted by the method of fluorescence in situ hybridization (FISH) as described in Heng and Tsui (1994) Meth. Molec. Biol. 33:109-122, using the various full-length (DTLRs 2-4) or partial (DTLR5) cDNA clones as probes. These analyses
- 20 were performed as a service by SeeDNA Biotech Inc. (Ontario, Canada). A search for human syndromes (or mouse defects in syntenic loci) associated with the mapped DTLR genes was conducted in the Dysmorphic Human-Mouse Homology Database by internet server
- 25 ([http://www.hgmp.mrc.ac.uk/DHMHHD/hum\\_chromel.html](http://www.hgmp.mrc.ac.uk/DHMHHD/hum_chromel.html)).

Conserved architecture of insect and human DTLR ectodomains.

- 30 The Toll family in *Drosophila* comprises at least four distinct gene products: Toll, the prototype receptor involved in dorsoventral patterning of the fly embryo (Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399) and a second named '18 Wheeler' (18w) that may also be involved in early embryonic development (Chiang and
- 35 Beachy (1994) Mech. Develop. 47:225-239; Eldon, et al. (1994) Develop. 120:885-899); two additional receptors are predicted by incomplete, Toll-like ORFs downstream of

the male-specific-transcript (Mst) locus (Genbank code X67703) or encoded by the 'sequence-tagged-site' (STS) Dm2245 (Genbank code G01378) (Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783). The extracellular segments  
5 of Toll and 18w are distinctively composed of imperfect, ~24 amino acid LRR motifs (Chiang and Beachy (1994) Mech. Develop. 47:225-239; and Eldon, et al. (1994) Develop. 120:885-899). Similar tandem arrays of LRRs commonly form the adhesive antennae of varied cell surface  
10 molecules and their generic tertiary structure is presumed to mimic the horseshoe-shaped cradle of a ribonuclease inhibitor fold, where seventeen LRRs show a repeating  $\beta/\alpha$ -hairpin, 28 residue motif (Buchanan and Gay (1996) Prog. Biophys. Molec. Biol. 65:1-44). The  
15 specific recognition of Spätzle by Toll may follow a model proposed for the binding of cystine-knot fold glycoprotein hormones by the multi-LRR ectodomains of serpentine receptors, using the concave side of the curved  $\beta$ -sheet (Kajava, et al. (1995) Structure 3:867-  
20 877); intriguingly, the pattern of cysteines in Spätzle, and an orphan Drosophila ligand, Trunk, predict a similar cystine-knot tertiary structure (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Casanova, et al. (1995) Genes Develop. 9:2539-2544).  
25       The 22 and 31 LRR ectodomains of Toll and 18w, respectively (the Mst ORF fragment displays 16 LRRs), are most closely related to the comparable 18, 19, 24, and 22 LRR arrays of DTLRs 1-4 (the incomplete DTLR5 chain presently includes four membrane-proximal LRRs) by  
30 sequence and pattern analysis (Altschul, et al. (1994) Nature Genet. 6:119-129; and Bork and Gibson (1996) Meth. Enzymol. 266:162-184) (Fig. 1). However, a striking difference in the human DTLR chains is the common loss of  
35 a ~90-residue cysteine-rich region that is variably embedded in the ectodomains of Toll, 18w and the Mst ORF (distanced four, six and two LRRs, respectively, from the membrane boundary). These cysteine clusters are

bipartite, with distinct 'top' (ending an LRR) and 'bottom' (stacked atop an LRR) halves (Chiang and Beachy (1994) Mech. Develop. 47:225-239; Eldon, et al. (1994) Develop. 120:885-899; and ,Buchanan and Gay (1996) Prog. Biophys. Molec. Biol. 65:1-44); the 'top' module recurs in both Drosophila and human DTLRs as a conserved juxtamembrane spacer (Fig. 1). We suggest that the flexibly located cysteine clusters in Drosophila receptors (and other LRR proteins), when mated 'top' to 'bottom', form a compact module with paired termini that can be inserted between any pair of LRRs without altering the overall fold of DTLR ectodomains; analogous 'extruded' domains decorate the structures of other proteins (Russell (1994) Protein Engin. 7:1407-1410).

#### Molecular design of the TH signaling domain.

Sequence comparison of Toll and IL-1 type-I (IL-1R1) receptors has disclosed a distant resemblance of a ~200 amino acid cytoplasmic domain that presumably mediates signaling by similar Rel-type transcription factors. Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; and Wasserman (1993) Molec. Biol. Cell 4:767-771). More recent additions to this functional paradigm include a pair of plant disease resistance proteins from tobacco and flax that feature an N-terminal TH module followed by nucleotide-binding (NTPase) and LRR segments (Wilson, et al. (1997) Curr. Biol. 7:175-178); by contrast, a 'death domain' preceeds the TH chain of MyD88, an intracellular myeloid differentiation marker (Mitcham, et al. (1996) J. Biol. Chem. 271:5777-5783; and Hardiman, et al. (1996) Oncogene 13:2467-2475) (Fig. 1). New IL-1-type receptors include IL-1R3, an accessory signaling molecule, and orphan receptors IL-1R4 (also called ST2/Fit-1/T1), IL-1R5 (IL-1R-related protein), and IL-1R6 (IL-1R-related protein-2) (Mitcham, et al. (1996) J. Biol. Chem. 271:5777-

5783;Hardiman, et al. (1996) Oncogene 13:2467-2475).

With the new human DTLR sequences, we have sought a structural definition of this evolutionary thread by analyzing the conformation of the common TH module: ten  
5 blocks of conserved sequence comprising 128 amino acids form the minimal TH domain fold; gaps in the alignment mark the likely location of sequence and length-variable loops (Fig. 2a).

Two prediction algorithms that take advantage of the  
10 patterns of conservation and variation in multiply aligned sequences, PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310), produced strong, concordant results for the TH signaling module (Fig. 2a). Each block contains a  
15 discrete secondary structural element: the imprint of alternating  $\beta$ -strands (labeled A-E) and  $\alpha$ -helices (numbered 1-5) is diagnostic of an  $\beta/\alpha$ -class fold with  $\alpha$ -helices on both faces of a parallel  $\beta$ -sheet. Hydrophobic  
20  $\beta$ -strands A, C and D are predicted to form 'interior' staves in the  $\beta$ -sheet, while the shorter, amphipathic  $\beta$ -strands B and E resemble typical 'edge' units (Fig. 2a). This assignment is consistent with a strand order of B-A-C-D-E in the core  $\beta$ -sheet (Fig. 2b); fold comparison ('mapping') and recognition ('threading') programs  
25 (Fischer, et al. (1996) FASEB J. 10:126-136) strongly return this doubly wound  $\beta/\alpha$  topology. A surprising, functional prediction of this outline structure for the TH domain is that many of the conserved, charged residues in the multiple alignment map to the C-terminal end of  
30 the  $\beta$ -sheet: residue Asp16 (block numbering scheme - Fig. 2a) at the end of  $\beta$ A, Arg39 and Asp40 following  $\beta$ B, Glu75 in the first turn of  $\alpha$ 3, and the more loosely conserved Glu/Asp residues in the  $\beta$ D- $\alpha$ 4 loop, or after  $\beta$ E (Fig. 2a). The location of four other conserved residues  
35 (Asp7, Glu28, and the Arg57-Arg/Lys58 pair) is compatible with a salt bridge network at the opposite, N-terminal end of the  $\beta$ -sheet (Fig. 2a).

Signaling function depends on the structural integrity of the TH domain. Inactivating mutations or deletions within the module boundaries (Fig. 2a) have been catalogued for IL-1R1 and Toll. Heguy, et al. (1992) J. Biol. Chem. 267:2605-2609; Croston, et al. (1995) J. Biol. Chem. 270:16514-16517; Schneider, et al. (1991) Genes Develop. 5:797-807; Norris and Manley. (1992) Genes Develop. 6:1654-1667; Norris and Manley (1995) Genes Develop. 9:358-369; and Norris and Manley (1996) Genes Develop. 10:862-872. The human DTLR1-5 chains extending past the minimal TH domain (8, 0, 6, 22 and 18 residue lengths, respectively) are most closely similar to the stubby, 4 aa 'tail' of the Mst ORF. Toll and 18w display unrelated 102 and 207 residue tails (Fig. 2a) that may negatively regulate the signaling of the fused TH domains. Norris and Manley (1995) Genes Develop. 9:358-369; and Norris and Manley (1996) Genes Develop. 10:862-872.

The evolutionary relationship between the disparate proteins that carry the TH domain can best be discerned by a phylogenetic tree derived from the multiple alignment (Fig. 3). Four principal branches segregate the plant proteins, the MyD88 factors, IL-1 receptors and Toll-like molecules; the latter branch clusters the *Drosophila* and human DTLRs.

#### Chromosomal dispersal of human DTLR genes.

In order to investigate the genetic linkage of the nascent human DTLR gene family, we mapped the chromosomal loci of four of the five genes by FISH (Fig. 4). The DTLR1 gene has previously been charted by the human genome project: an STS database locus (dbSTS accession number G06709, corresponding to STS WI-7804 or SHGC-12827) exists for the Humrsc786 cDNA (Nomura, et al. (1994) DNA Res 1:27-35) and fixes the gene to chromosome 4 marker interval D4S1587-D42405 (50-56 cM) circa 4p14. This assignment has recently been corroborated by FISH

analysis. Taguchi, et al. (1996) Genomics 32:486-488. In the present work, we reliably assign the remaining DTLR genes to loci on chromosome 4q32 (DTLR2), 4q35 (DTLR3), 9q32-33 (DTLR4) and 1q33.3 (DTLR5). During the  
5 course of this work, an STS for the parent DTLR2 EST (cloneID # 80633) has been generated (dbSTS accession number T57791 for STS SHGC-33147) and maps to the chromosome 4 marker interval D4S424-D4S1548 (143-153 cM) at 4q32 -in accord with our findings. There is a ~50 cM  
10 gap between DTLR2 and DTLR3 genes on the long arm of chromosome 4.

DTLR genes are differentially expressed.  
Both Toll and 18w have complex spatial and temporal  
15 patterns of expression in *Drosophila* that may point to functions beyond embryonic patterning. St. Johnston and Nüsslein-Volhard (1992) Cell 68:201-219; Morisato and Anderson (1995) Ann. Rev. Genet. 29:371-399; Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416;  
20 Lemaitre, et al. (1996) Cell 86:973-983; Chiang and Beachy (1994) Mech. Develop. 47:225-239; and Eldon, et al. (1994) Develop. 120:885-899. We have examined the spatial distribution of DTLR transcripts by mRNA blot analysis with varied human tissue and cancer cell lines  
25 using radioabeled DTLR cDNAs (Fig. 5). DTLR1 is found to be ubiquitously expressed, and at higher levels than the other receptors. Presumably reflecting alternative splicing, 'short' 3.0 kB and 'long' 8.0 kB DTLR1 transcript forms are present in ovary and spleen,  
30 respectively (Fig. 5, panels A & B). A cancer cell mRNA panel also shows the prominent overexpression of DTLR1 in a Burkitt's Lymphoma Raji cell line (Fig. 5, panel C). DTLR2 mRNA is less widely expressed than DTLR1, with a 4.0 kB species detected in lung and a 4.4 kB transcript  
35 evident in heart, brain and muscle. The tissue distribution pattern of DTLR3 echoes that of DTLR2 (Fig. 5, panel E). DTLR3 is also present as two major

transcripts of approximately 4.0 and 6.0 kB in size, and the highest levels of expression are observed in placenta and pancreas. By contrast, DTLR4 and DTLR5 messages appear to be extremely tissue-specific. DTLR4 was  
5 detected only in placenta as a single transcript of ~7.0 kB in size. A faint 4.0 kB signal was observed for DTLR5 in ovary and peripheral blood monocytes.

10 Components of an evolutionarily ancient regulatory system.

The original molecular blueprints and divergent fates of signaling pathways can be reconstructed by comparative genomic approaches. Miklos and Rubin (1996) Cell 86:521-529; Chothia (1994) Develop. 1994 Suppl., 27-  
15 33; Banfi, et al. (1996) Nature Genet. 13:167-174; and Wang, et al. (1996) J. Biol. Chem. 271:4468-4476. We have used this logic to identify an emergent gene family in humans, encoding five receptor paralogs at present, DTLRs 1-5, that are the direct evolutionary counterparts  
20 of a *Drosophila* gene family headed by Toll (Figs. 1-3). The conserved architecture of human and fly DTLRs, conserved LRR ectodomains and intracellular TH modules (Fig. 1), intimates that the robust pathway coupled to Toll in *Drosophila* (6, 7) survives in vertebrates. The  
25 best evidence borrows from a reiterated pathway: the manifold IL-1 system and its repertoire of receptor-fused TH domains, IRAK, NF- $\kappa$ B and I- $\kappa$ B homologs (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; Wasserman (1993) Molec. Biol. Cell 4:767-771; Hardiman,  
30 et al. (1996) Oncogene 13:2467-2475; and Cao, et al. (1996) Science 271:1128-1131); a Tube-like factor has also been characterized. It is not known whether DTLRs can productively couple to the IL-1R signaling machinery, or instead, a parallel set of proteins is used.  
35 Differently from IL-1 receptors, the LRR cradle of human DTLRs is predicted to retain an affinity for Spätzle/Trunk-related cystine-knot factors; candidate



DTLR ligands (called PENS) that fit this mold have been isolated.

Biochemical mechanisms of signal transduction can be gauged by the conservation of interacting protein folds in a pathway. Miklos and Rubin (1996) Cell 86:521-529; Chothia (1994) Develop. 1994 Suppl., 27-33. At present, the Toll signaling paradigm involves some molecules whose roles are narrowly defined by their structures, actions or fates: Pelle is a Ser/Thr kinase (phosphorylation), Dorsal is an NF- $\kappa$ B-like transcription factor (DNA-binding) and Cactus is an ankyrin-repeat inhibitor (Dorsal binding, degradation). Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416. By contrast, the functions of the Toll TH domain and Tube remain enigmatic. Like other cytokine receptors (Heldin (1995) Cell 80:213-223), ligand-mediated dimerization of Toll appears to be the triggering event: free cysteines in the juxtamembrane region of Toll create constitutively active receptor pairs (Schneider, et al. (1991) Genes Develop. 5:797-807), and chimeric Torso-Toll receptors signal as dimers (Galindo, et al. (1995) Develop. 121:2209-2218); yet, severe truncations or wholesale loss of the Toll ectodomain results in promiscuous intracellular signaling (Norris and Manley (1995) Genes Develop. 9:358-369; and Winans and Hashimoto (1995) Molec. Biol. Cell 6:587-596), reminiscent of oncogenic receptors with catalytic domains (Heldin (1995) Cell 80:213-223). Tube is membrane-localized, engages the N-terminal (death) domain of Pelle and is phosphorylated, but neither Toll-Tube or Toll-Pelle interactions are registered by two-hybrid analysis (Galindo, et al. (1995) Develop. 121:2209-2218; and Großhans, et al. (1994) Nature 372:563-566); this latter result suggests that the conformational 'state' of the Toll TH domain somehow affects factor recruitment. Norris and Manley (1996) Genes Develop. 10:862-872; and Galindo, et al. (1995) Develop. 121:2209-2218.

At the heart of these vexing issues is the structural nature of the Toll TH module. To address this question, we have taken advantage of the evolutionary diversity of TH sequences from insects, plants and  
5 vertebrates, incorporating the human DTLR chains, and extracted the minimal, conserved protein core for structure prediction and fold recognition (Fig. 2). The strongly predicted ( $\beta/\alpha$ )<sub>5</sub> TH domain fold with its asymmetric cluster of acidic residues is topologically  
10 identical to the structures of response regulators in bacterial two-component signaling pathways (Volz (1993) Biochemistry 32:11741-11753; and Parkinson (1993) Cell 73:857-871) (Fig. 2). The prototype chemotaxis regulator CheY transiently binds a divalent cation in an 'aspartate  
15 pocket' at the C-end of the core  $\beta$ -sheet; this cation provides electrostatic stability and facilitates the activating phosphorylation of an invariant Asp. Volz (1993) Biochemistry 32:11741-11753. Likewise, the TH domain may capture cations in its acidic nest, but  
20 activation, and downstream signaling, could depend on the specific binding of a negatively charged moiety: anionic ligands can overcome intensely negative binding-site potentials by locking into precise hydrogen-bond networks. Ledvina, et al. (1996) Proc. Natl. Acad. Sci.  
25 USA 93:6786-6791. Intriguingly, the TH domain may not simply act as a passive scaffold for the assembly of a Tube/Pelle complex for Toll, or homologous systems in plants and vertebrates, but instead actively participate as a true conformational trigger in the signal  
30 transducing machinery. Perhaps explaining the conditional binding of a Tube/Pelle complex, Toll dimerization could promote unmasking, by regulatory receptor tails (Norris and Manley (1995) Genes Develop. 9:358-369; Norris and Manley (1996) Genes Develop.  
35 10:862-872), or binding by small molecule activators of the TH pocket. However, 'free' TH modules inside the cell (Norris and Manley (1995) Genes Develop. 9:358-369;

Winans and Hashimoto (1995) Molec. Biol. Cell 6:587-596) could act as catalytic, CheY-like triggers by activating and docking with errant Tube/Pelle complexes.

5 Morphogenetic receptors and immune defense.

The evolutionary link between insect and vertebrate immune systems is stamped in DNA: genes encoding antimicrobial factors in insects display upstream motifs similar to acute phase response elements known to bind NF- $\kappa$ B transcription factors in mammals. Hultmark (1993) Trends Genet. 9:178-183. Dorsal, and two Dorsal-related factors, Dif and Relish, help induce these defense proteins after bacterial challenge (Reichhart, et al. (1993) C. R. Acad. Sci. Paris 316:1218-1224; Ip, et al. (1993) Cell 75:753-763; and Dushay, et al. (1996) Proc. Natl. Acad. Sci. USA 93:10343-10347); Toll, or other DTLRs, likely modulate these rapid immune responses in adult *Drosophila* (Lemaitre, et al. (1996) Cell 86:973-983; and Rosetto, et al. (1995) Biochem. Biophys. Res. Commun. 209:111-116). These mechanistic parallels to the IL-1 inflammatory response in vertebrates are evidence of the functional versatility of the Toll signaling pathway, and suggest an ancient synergy between embryonic patterning and innate immunity (Belvin and Anderson (1996) Ann. Rev. Cell Develop. Biol. 12:393-416; Lemaitre, et al. (1996) Cell 86:973-983; Wasserman (1993) Molec. Biol. Cell 4:767-771; Wilson, et al. (1997) Curr. Biol. 7:175-178; Hultmark (1993) Trends Genet. 9:178-183; Reichhart, et al. (1993) C. R. Acad. Sci. Paris 316:1218-1224; Ip, et al. (1993) Cell 75:753-763; Dushay, et al. (1996) Proc. Natl. Acad. Sci. USA 93:10343-10347; Rosetto, et al. (1995) Biochem. Biophys. Res. Commun. 209:111-116; Medzhitov and Janeway (1997) Curr. Opin. Immunol. 9:4-9; and Medzhitov and Janeway (1997) Curr. Opin. Immunol. 9:4-9). The closer homology of insect and human DTLR proteins invites an even stronger overlap of biological functions that supersedes the purely immune

parallels to IL-1 systems, and lends potential molecular regulators to dorso-ventral and other transformations of vertebrate embryos. DeRobertis and Sasai (1996) Nature 380:37-40; and Arendt and Nübler-Jung (1997) Mech.

5 Develop. 61:7-21.

The present description of an emergent, robust receptor family in humans mirrors the recent discovery of the vertebrate Frizzled receptors for Wnt patterning factors. Wang, et al. (1996) J. Biol. Chem. 271:4468-  
10 4476. As numerous other cytokine-receptor systems have roles in early development (Lemaire and Kodjabachian (1996) Trends Genet. 12:525-531), perhaps the distinct cellular contexts of compact embryos and gangly adults simply result in familiar signaling pathways and their  
15 diffusible triggers having different biological outcomes at different times, e.g., morphogenesis versus immune defense for DTLRs. For insect, plant, and human Toll-related systems (Hardiman, et al. (1996) Oncogene 13:2467-2475; Wilson, et al. (1997) Curr. Biol. 7:175-  
20 178), these signals course through a regulatory TH domain that intriguingly resembles a bacterial transducing engine (Parkinson (1993) Cell 73:857-871).

In particular, the DTLR6 exhibits structural features which establish its membership in the family.  
25 Moreover, members of the family have been implicated in a number of significant developmental disease conditions and with function of the innate immune system. In particular, the DTLR6 has been mapped to the X chromosome to a location which is a hot spot for major developmental  
30 abnormalities. See, e.g., The Sanger Center: human X chromosome website <http://www.sanger.ac.uk/HGP/ChrX/index.shtml>; and the Baylor College of Medicine Human Genome Sequencing website <http://gc.bcm.tmc.edu:8088/cgi-bin/seq/home>.

35 The accession number for the deposited PAC is AC003046. This accession number contains sequence from two PACs: RPC-164K3 and RPC-263P4. These two PAC

sequences mapped on human chromosome Xp22 at the Baylor web site between STS markers DXS704 and DXS7166. This region is a "hot spot" for severe developmental abnormalities.

5

### III. Amplification of DTLR fragment by PCR

Two appropriate primer sequences are selected (see Tables 1 through 10). RT-PCR is used on an appropriate mRNA sample selected for the presence of message to produce a partial or full length cDNA, e.g., a sample which expresses the gene. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (1995; eds.) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY. Such will allow determination of a useful sequence to probe for a full length gene in a cDNA library. The TLR6 is a contiguous sequence in the genome, which may suggest that the other TLRs are also. Thus, PCR on genomic DNA may yield full length contiguous sequence, and chromosome walking methodology would then be applicable. Alternatively, sequence databases will contain sequence corresponding to portions of the described embodiments, or closely related forms, e.g., alternative splicing, etc. Expression cloning techniques also may be applied on cDNA libraries.

### IV. Tissue distribution of DTLRs

Message for each gene encoding these DTLRs has been detected. See Figures 5A-5F. Other cells and tissues will be assayed by appropriate technology, e.g., PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations are available, e.g., from Clontech, Mountain View, CA. Identification of sources of natural expression are useful, as described.

Southern Analysis: DNA (5 µg) from a primary amplified cDNA library is digested with appropriate restriction enzymes to release the inserts, run on a 1% agarose gel and

transferred to a nylon membrane (Schleicher and Schuell, Keene, NH).

Samples for human mRNA isolation would typically include, e.g.: peripheral blood mononuclear cells  
5 (monocytes, T cells, NK cells, granulocytes, B cells), resting (T100); peripheral blood mononuclear cells, activated with anti-CD3 for 2, 6, 12 h pooled (T101); T cell, TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6,  
10 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic  
15 treated with specific peptide for 2, 6, 12 h pooled (T109); T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111); T cells CD4+CD45RO- T cells polarized 27 days in anti-CD28, IL-4, and anti IFN- $\gamma$ , TH2  
20 polarized, activated with anti-CD3 and anti-CD28 4 h (T116); T cell tumor lines Jurkat and Hut78, resting (T117); T cell clones, pooled AD130.2, Tc783.12, Tc783.13, Tc783.58, Tc782.69, resting (T118); T cell random  $\gamma\delta$  T cell clones, resting (T119); Splenocytes,  
25 resting (B100); Splenocytes, activated with anti-CD40 and IL-4 (B101); B cell EBV lines pooled WT49, RSB, JY, CVIR, 721.221, RM3, HSY, resting (B102); B cell line JY, activated with PMA and ionomycin for 1, 6 h pooled (B103); NK 20 clones pooled, resting (K100); NK 20 clones  
30 pooled, activated with PMA and ionomycin for 6 h (K101); NKL clone, derived from peripheral blood of LGL leukemia patient, IL-2 treated (K106); NK cytotoxic clone 640-A30-1, resting (K107); hematopoietic precursor line TF1, activated with PMA and ionomycin for 1, 6 h pooled  
35 (C100); U937 premonocytic line, resting (M100); U937 premonocytic line, activated with PMA and ionomycin for 1, 6 h pooled (M101); elutriated monocytes, activated

with LPS, IFN $\gamma$ , anti-IL-10 for 1, 2, 6, 12, 24 h pooled (M102); elutriated monocytes, activated with LPS, IFN $\gamma$ , IL-10 for 1, 2, 6, 12, 24 h pooled (M103); elutriated monocytes, activated with LPS, IFN $\gamma$ , anti-IL-10 for 4, 16 h pooled (M106); elutriated monocytes, activated with LPS, IFN $\gamma$ , IL-10 for 4, 16 h pooled (M107); elutriated monocytes, activated LPS for 1 h (M108); elutriated monocytes, activated LPS for 6 h (M109); DC 70% CD1a+, from CD34+ GM-CSF, TNF $\alpha$  12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNF $\alpha$  12 days, activated with PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNF $\alpha$  12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNF $\alpha$  12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D104); DC 95% CD14+, ex CD34+ GM-CSF, TNF $\alpha$  12 days FACS sorted, activated with PMA and ionomycin 1, 6 hr pooled (D105); DC CD1a+ CD86+, from CD34+ GM-CSF, TNF $\alpha$  12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D106); DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-CSF, IL-4 5 days, resting (D108); DC from monocytes GM-CSF, IL-4 5 days, activated LPS 4, 16 h pooled (D109); DC from monocytes GM-CSF, IL-4 5 days, activated TNF $\alpha$ , monocyte supe for 4, 16 h pooled (D110); leiomyoma L11 benign tumor (X101); normal myometrium M5 (O115); malignant leiomyosarcoma GS1 (X103); lung fibroblast sarcoma line MRC5, activated with PMA and ionomycin for 1, 6 h pooled (C101); kidney epithelial carcinoma cell line CHA, activated with PMA and ionomycin for 1, 6 h pooled (C102); kidney fetal 28 wk male (O100); lung fetal 28 wk male (O101); liver fetal 28 wk male (O102); heart fetal 28 wk male (O103); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); small intestine fetal 28 wk male (O107); adipose tissue fetal 28 wk male (O108); ovary fetal 25 wk female (O109); uterus fetal 25 wk female (O110); testes fetal 28 wk male

(O111); spleen fetal 28 wk male (O112); adult placenta 28 wk (O113); and tonsil inflamed, from 12 year old (X100).

Samples for mouse mRNA isolation can include, e.g.:  
resting mouse fibroblastic L cell line (C200); Braf:ER  
5 (Braf fusion to estrogen receptor) transfected cells,  
control (C201); T cells, TH1 polarized (Mel14 bright,  
CD4+ cells from spleen, polarized for 7 days with IFN- $\gamma$   
and anti IL-4; T200); T cells, TH2 polarized (Mel14  
bright, CD4+ cells from spleen, polarized for 7 days with  
10 IL-4 and anti-IFN- $\gamma$ ; T201); T cells, highly TH1 polarized  
(see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367;  
activated with anti-CD3 for 2, 6, 16 h pooled; T202); T  
cells, highly TH2 polarized (see Openshaw, et al. (1995)  
J. Exp. Med. 182:1357-1367; activated with anti-CD3 for  
15 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted  
from thymus (T204); TH1 T cell clone D1.1, resting for 3  
weeks after last stimulation with antigen (T205); TH1 T  
cell clone D1.1, 10  $\mu$ g/ml ConA stimulated 15 h (T206);  
TH2 T cell clone CDC35, resting for 3 weeks after last  
20 stimulation with antigen (T207); TH2 T cell clone CDC35,  
10  $\mu$ g/ml ConA stimulated 15 h (T208); Mel14+ naive T  
cells from spleen, resting (T209); Mel14+ T cells,  
polarized to Th1 with IFN- $\gamma$ /IL-12/anti-IL-4 for 6, 12, 24  
h pooled (T210); Mel14+ T cells, polarized to Th2 with  
25 IL-4/anti-IFN- $\gamma$  for 6, 13, 24 h pooled (T211);  
unstimulated mature B cell leukemia cell line A20 (B200);  
unstimulated B cell line CH12 (B201); unstimulated large  
B cells from spleen (B202); B cells from total spleen,  
LPS activated (B203); metrizamide enriched dendritic  
30 cells from spleen, resting (D200); dendritic cells from  
bone marrow, resting (D201); monocyte cell line RAW 264.7  
activated with LPS 4 h (M200); bone-marrow macrophages  
derived with GM and M-CSF (M201); macrophage cell line  
J774, resting (M202); macrophage cell line J774 + LPS +  
35 anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203);  
macrophage cell line J774 + LPS + IL-10 at 0.5, 1, 3, 5,  
12 h pooled (M204); aerosol challenged mouse lung tissue,



Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled  
(see Garlisi, et al. (1995) Clinical Immunology and  
Immunopathology 75:75-83; X206); Nippostrongylus-infected  
lung tissue (see Coffman, et al. (1989) Science 245:308-  
5 310; X200); total adult lung, normal (O200); total lung,  
rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-  
252; O205); IL-10 K.O. spleen (see Kuhn, et al. (1991)  
Cell 75:263-274; X201); total adult spleen, normal  
(O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's  
10 patches (O202); total Peyer's patches, normal (O210); IL-  
10 K.O. mesenteric lymph nodes (X203); total mesenteric  
lymph nodes, normal (O211); IL-10 K.O. colon (X203);  
total colon, normal (O212); NOD mouse pancreas (see  
Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205);  
15 total thymus, rag-1 (O208); total kidney, rag-1 (O209);  
total heart, rag-1 (O202); total brain, rag-1 (O203);  
total testes, rag-1 (O204); total liver, rag-1 (O206);  
rat normal joint tissue (O300); and rat arthritic joint  
tissue (X300).

20

#### V. Cloning of species counterparts of DTLRs

Various strategies are used to obtain species  
counterparts of these DTLRs, preferably from other  
25 primates. One method is by cross hybridization using  
closely related species DNA probes. It may be useful to  
go into evolutionarily similar species as intermediate  
steps. Another method is by using specific PCR primers  
based on the identification of blocks of similarity or  
30 difference between particular species, e.g., human,  
genes, e.g., areas of highly conserved or nonconserved  
polypeptide or nucleotide sequence. Alternatively,  
antibodies may be used for expression cloning.

#### 35 VI. Production of mammalian DTLR protein

An appropriate, e.g., GST, fusion construct is  
engineered for expression, e.g., in *E. coli*. For

example, a mouse IGIF pGex plasmid is constructed and transformed into *E. coli*. Freshly transformed cells are grown in LB medium containing 50 µg/ml ampicillin and induced with IPTG (Sigma, St. Louis, MO). After  
5 overnight induction, the bacteria are harvested and the pellets containing the DTLR protein are isolated. The pellets are homogenized in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and 2 mM pefabloc) in 2 liters. This material is passed through a microfluidizer  
10 (Microfluidics, Newton, MA) three times. The fluidized supernatant is spun down on a Sorvall GS-3 rotor for 1 h at 13,000 rpm. The resulting supernatant containing the DTLR protein is filtered and passed over a glutathione-SEPHAROSE column equilibrated in 50 mM Tris-base pH 8.0.  
15 The fractions containing the DTLR-GST fusion protein are pooled and cleaved with thrombin (Enzyme Research Laboratories, Inc., South Bend, IN). The cleaved pool is then passed over a Q-SEPHAROSE column equilibrated in 50 mM Tris-base. Fractions containing DTLR are pooled and  
20 diluted in cold distilled H<sub>2</sub>O, to lower the conductivity, and passed back over a fresh Q-Sepharose column, alone or in succession with an immunoaffinity antibody column.. Fractions containing the DTLR protein are pooled, aliquoted, and stored in the -70° C freezer.  
25       Comparision of the CD spectrum with DTLR1 protein may suggest that the protein is correctly folded. See Hazuda, et al. (1969) J. Biol. Chem. 264:1689-1693.

#### VII. Biological Assays with DTLRs

30       Biological assays will generally be directed to the ligand binding feature of the protein or to the kinase/phosphatase activity of the receptor. The activity will typically be reversible, as are many other enzyme actions. mediate phosphatase or phosphorylase  
35 activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II,

Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and  
5 Parker, et al. (1993) Nature 363:736-738.

The family of interleukins 1 contains molecules, each of which is an important mediator of inflammatory disease. For a comprehensive review, see Dinarello (1996) "Biologic basis for interleukin-1 in disease"  
10 Blood 87:2095-2147. There are suggestions that the various Toll ligands may play important roles in the initiation of disease, particularly inflammatory responses. The finding of novel proteins related to the IL-1 family furthers the identification of molecules that  
15 provide the molecular basis for initiation of disease and allow for the development of therapeutic strategies of increased range and efficacy.

VIII. Preparation of antibodies specific for, e.g.,  
20 DTLR4

Inbred Balb/c mice are immunized intraperitoneally with recombinant forms of the protein, e.g., purified DTLR4 or stable transfected NIH-3T3 cells. Animals are boosted at appropriate time points with protein, with or  
25 without additional adjuvant, to further stimulate antibody production. Serum is collected, or hybridomas produced with harvested spleens.

Alternatively, Balb/c mice are immunized with cells transformed with the gene or fragments thereof, either  
30 endogenous or exogenous cells, or with isolated membranes enriched for expression of the antigen. Serum is collected at the appropriate time, typically after numerous further administrations. Various gene therapy techniques may be useful, e.g., in producing protein in  
35 situ, for generating an immune response.

Monoclonal antibodies may be made. For example, splenocytes are fused with an appropriate fusion partner

and hybridomas are selected in growth medium by standard procedures. Hybridoma supernatants are screened for the presence of antibodies which bind to the desired DTLR, e.g., by ELISA or other assay. Antibodies which  
5 specifically recognize specific DTLR embodiments may also be selected or prepared.

In another method, synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan  
10 (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a  
15 substrate for panning methods. Nucleic acids may also be introduced into cells in an animal to produce the antigen, which serves to elicit an immune response. See, e.g., Wang, et al. (1993) Proc. Nat'l. Acad. Sci. 90:4156-4160; Barry, et al. (1994) BioTechniques 16:616-  
20 619; and Xiang, et al. (1995) Immunity 2: 129-135.

#### IX. Production of fusion proteins with, e.g., DTLR5

Various fusion constructs are made with DTLR5. This portion of the gene is fused to an epitope tag, e.g., a  
25 FLAG tag, or to a two hybrid system construct. See, e.g., Fields and Song (1989) Nature 340:245-246.

The epitope tag may be used in an expression cloning procedure with detection with anti-FLAG antibodies to detect a binding partner, e.g., ligand for the respective  
30 DTLR5. The two hybrid system may also be used to isolate proteins which specifically bind to DTLR5.

#### X. Chromosomal mapping of DTLRs

Chromosome spreads are prepared. In situ  
35 hybridization is performed on chromosome preparations obtained from phytohemagglutinin-stimulated lymphocytes cultured for 72 h. 5-bromodeoxyuridine is added for the

final seven hours of culture (60 µg/ml of medium), to ensure a posthybridization chromosomal banding of good quality.

5 An appropriate fragment, e.g., a PCR fragment, amplified with the help of primers on total B cell cDNA template, is cloned into an appropriate vector. The vector is labeled by nick-translation with <sup>3</sup>H. The radiolabeled probe is hybridized to metaphase spreads as described in Mattei, et al. (1985) Hum. Genet. 69:327-  
10 331.

After coating with nuclear track emulsion (KODAK NTB2), slides are exposed, e.g., for 18 days at 4° C. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with  
15 buffered Giemsa solution and metaphase photographed. R-banding is then performed by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis.

Alternatively, FISH can be performed, as described  
20 above. The DTLR genes are located on different chromosomes. DTLR2 and DTLR3 are localized to human chromosome 4; DTLR4 is localized to human chromosome 9, and DTLR5 is localized to human chromosome 1. See Figures 4A-4D.

## 25 XI. Structure activity relationship

Information on the criticality of particular residues is determined using standard procedures and analysis. Standard mutagenesis analysis is performed,  
30 e.g., by generating many different variants at determined positions, e.g., at the positions identified above, and evaluating biological activities of the variants. This may be performed to the extent of determining positions which modify activity, or to focus on specific positions  
35 to determine the residues which can be substituted to either retain, block, or modulate biological activity.

Alternatively, analysis of natural variants can indicate what positions tolerate natural mutations. This may result from populational analysis of variation among individuals, or across strains or species. Samples from  
5 selected individuals are analysed, e.g., by PCR analysis and sequencing. This allows evaluation of population polymorphisms.

#### XI. Isolation of a ligand for a DTLR

10 A DTLR can be used as a specific binding reagent to identify its binding partner, by taking advantage of its specificity of binding, much like an antibody would be used. A binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to  
15 a substrate for panning methods.

The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, i.e., ligand, preferably membrane associated. Standard staining techniques are used to  
20 detect or sort surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

25 For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at  $2-3 \times 10^5$  cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

30 On day 1 for each sample, prepare 0.5 ml of a solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is prepared, e.g., of DTLR-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with  
35 serum free DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in

DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1 M NaN<sub>3</sub> for 20 min. Cells are then washed with HBSS/saponin 1X. Add appropriate DTLR or DTLR/antibody complex to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. If appropriate, add first antibody for 30 min. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H<sub>2</sub>O<sub>2</sub> per 5 ml of glass distilled water.

Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

Evaluate positive staining of pools and progressively subclone to isolation of single genes responsible for the binding.

Alternatively, DTLR reagents are used to affinity purify or sort out cells expressing a putative ligand. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as described above. The ligand can be immobilized and used

to immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of a DTLR fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and amplification lead to enrichment of appropriate clones and eventual isolation of receptor expressing clones.

Phage expression libraries can be screened by mammalian DTLRs. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled; and the invention is not to be limited by the specific embodiments that have been presented herein by way of example.



## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- 5 (i) APPLICANT: (A) NAME: Schering Corporation  
(B) STREET: 2000 Galloping Hill Road  
(C) CITY: Kenilworth  
10 (D) STATE: New Jersey  
(E) COUNTRY: USA  
(F) POSTAL CODE: 07033  
(G) TELEPHONE: (908) 298-4000  
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- 15 (ii) TITLE OF INVENTION: HUMAN RECEPTOR PROTEINS; RELATED  
REAGENTS AND METHODS
- (iii) NUMBER OF SEQUENCES: 35
- 20 (iv) COMPUTER READABLE FORM:  
(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: Macintosh Power PC  
(C) OPERATING SYSTEM: 8.0  
25 (D) SOFTWARE: Microsoft Word 6.0
- (v) CURRENT APPLICATION DATA:  
(A) APPLICATION NUMBER:  
(B) FILING DATE:  
30 (C) CLASSIFICATION:
- (vi) PRIOR APPLICATION DATA:  
(A) APPLICATION NO.: USSN 60/044,293  
(B) FILING DATE: 07-MAY-1997
- 35 (A) APPLICATION NO.: USSN 60/072,212  
(B) FILING DATE: 22-JAN-1998
- (A) APPLICATION NO.: USSN 60/076,947  
40 (B) FILING DATE: 05-MAR-1998

## (2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:  
45 (A) LENGTH: 2367 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- 50 (ix) FEATURE:  
(A) NAME/KEY: CDS  
(B) LOCATION: 1..2358
- 55 (ix) FEATURE:  
(A) NAME/KEY: mat\_peptide  
(B) LOCATION: 67..2358

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

5	ATG	ACT	AGC	ATC	TTC	CAT	TTT	GCC	ATT	ATC	TTC	ATG	TTA	ATA	CTT	CAG	48
	Met	Thr	Ser	Ile	Phe	His	Phe	Ala	Ile	Ile	Phe	Met	Leu	Ile	Leu	Gln	
	-22		-20					-15					-10				
10	ATC	AGA	ATA	CAA	TTA	TCT	GAA	GAA	AGT	GAA	TTT	TTA	GTT	GAT	AGG	TCA	96
	Ile	Arg	Ile	Gln	Leu	Ser	Glu	Glu	Ser	Glu	Phe	Leu	Val	Asp	Arg	Ser	
	-5						1				5					10	
15	AAA	AAC	GGT	CTC	ATC	CAC	GTT	CCT	AAA	GAC	CTA	TCC	CAG	AAA	ACA	ACA	144
	Lys	Asn	Gly	Leu	Ile	His	Val	Pro	Lys	Asp	Leu	Ser	Gln	Lys	Thr	Thr	
				15						20					25		
20	ATC	TTA	AAT	ATA	TCG	CAA	AAT	TAT	ATA	TCT	GAG	CTT	TGG	ACT	TCT	GAC	192
	Ile	Leu	Asn	Ile	Ser	Gln	Asn	Tyr	Ile	Ser	Glu	Leu	Trp	Thr	Ser	Asp	
				30					35					40			
25	ATC	TTA	TCA	CTG	TCA	AAA	CTG	AGG	ATT	TTG	ATA	ATT	TCT	CAT	AAT	AGA	240
	Ile	Leu	Ser	Leu	Ser	Lys	Leu	Arg	Ile	Leu	Ile	Ile	Ser	His	Asn	Arg	
			45					50					55				
30	ATC	CAG	TAT	CTT	GAT	ATC	AGT	GTT	TTC	AAA	TTC	AAC	CAG	GAA	TTG	GAA	288
	Ile	Gln	Tyr	Leu	Asp	Ile	Ser	Val	Phe	Lys	Phe	Asn	Gln	Glu	Leu	Glu	
	60						65					70					
35	TAC	TTG	GAT	TTG	TCC	CAC	AAC	AAG	TTG	GTG	AAG	ATT	TCT	TGC	CAC	CCT	336
	Tyr	Leu	Asp	Leu	Ser	His	Asn	Lys	Leu	Val	Lys	Ile	Ser	Cys	His	Pro	
	75					80					85					90	
40	ACT	GTG	AAC	CTC	AAG	CAC	TTG	GAC	CTG	TCA	TTT	AAT	GCA	TTT	GAT	GCC	384
	Thr	Val	Asn	Leu	Lys	His	Leu	Asp	Leu	Ser	Phe	Asn	Ala	Phe	Asp	Ala	
				95						100					105		
45	CTG	CCT	ATA	TGC	AAA	GAG	TTT	GGC	AAT	ATG	TCT	CAA	CTA	AAA	TTT	CTG	432
	Leu	Pro	Ile	Cys	Lys	Glu	Phe	Gly	Asn	Met	Ser	Gln	Leu	Lys	Phe	Leu	
				110				115						120			
50	GGG	TTG	AGC	ACC	ACA	CAC	TTA	GAA	AAA	TCT	AGT	GTG	CTG	CCA	ATT	GCT	480
	Gly	Leu	Ser	Thr	Thr	His	Leu	Glu	Lys	Ser	Ser	Val	Leu	Pro	Ile	Ala	
			125					130					135				
55	CAT	TTG	AAT	ATC	AGC	AAG	GTC	TTG	CTG	GTC	TTA	GGA	GAG	ACT	TAT	GGG	528
	His	Leu	Asn	Ile	Ser	Lys	Val	Leu	Leu	Val	Leu	Gly	Glu	Thr	Tyr	Gly	
	140					145						150					
60	GAA	AAA	GAA	GAC	CCT	GAG	GGC	CTT	CAA	GAC	TTT	AAC	ACT	GAG	AGT	CTG	576
	Glu	Lys	Glu	Asp	Pro	Glu	Gly	Leu	Gln	Asp	Phe	Asn	Thr	Glu	Ser	Leu	
	155					160					165					170	
65	CAC	ATT	GTG	TTC	CCC	ACA	AAC	AAA	GAA	TTC	CAT	TTT	ATT	TTG	GAT	GTG	624
	His	Ile	Val	Phe	Pro	Thr	Asn	Lys	Glu	Phe	His	Phe	Ile	Leu	Asp	Val	
					175					180					185		
70	TCA	GTC	AAG	ACT	GTA	GCA	AAT	CTG	GAA	CTA	TCT	AAT	ATC	AAA	TGT	GTG	672
	Ser	Val	Lys	Thr	Val	Ala	Asn	Leu	Glu	Leu	Ser	Asn	Ile	Lys	Cys	Val	
				190					195					200			
75	CTA	GAA	GAT	AAC	AAA	TGT	TCT	TAC	TTC	CTA	AGT	ATT	CTG	GCG	AAA	CTT	720
	Leu	Glu	Asp	Asn	Lys	Cys	Ser	Tyr	Phe	Leu	Ser	Ile	Leu	Ala	Lys	Leu	

	205	210	215	
5	CAA ACA AAT CCA AAG TTA TCA AGT CTT ACC TTA AAC AAC ATT GAA ACA Gln Thr Asn Pro Lys Leu Ser Ser Leu Thr Leu Asn Asn Ile Glu Thr 220 225 230			768
10	ACT TGG AAT TCT TTC ATT AGG ATC CTC CAA CTA GTT TGG CAT ACA ACT Thr Trp Asn Ser Phe Ile Arg Ile Leu Gln Leu Val Trp His Thr Thr 235 240 245 250			816
15	GTA TGG TAT TTC TCA ATT TCA AAC GTG AAG CTA CAG GGT CAG CTG GAC Val Trp Tyr Phe Ser Ile Ser Asn Val Lys Leu Gln Gly Gln Leu Asp 255 260 265			864
20	TTC AGA GAT TTT GAT TAT TCT GGC ACT TCC TTG AAG GCC TTG TCT ATA Phe Arg Asp Phe Asp Tyr Ser Gly Thr Ser Leu Lys Ala Leu Ser Ile 270 275 280			912
25	CAC CAA GTT GTC AGC GAT GTG TTC GGT TTT CCG CAA AGT TAT ATC TAT His Gln Val Val Ser Asp Val Phe Gly Phe Pro Gln Ser Tyr Ile Tyr 285 290 295			960
30	GAA ATC TTT TCG AAT ATG AAC ATC AAA AAT TTC ACA GTG TCT GGT ACA Glu Ile Phe Ser Asn Met Asn Ile Lys Asn Phe Thr Val Ser Gly Thr 300 305 310			1008
35	CGC ATG GTC CAC ATG CTT TGC CCA TCC AAA ATT AGC CCG TTC CTG CAT Arg Met Val His Met Leu Cys Pro Ser Lys Ile Ser Pro Phe Leu His 315 320 325 330			1056
40	TTG GAT TTT TCC AAT AAT CTC TTA ACA GAC ACG GTT TTT GAA AAT TGT Leu Asp Phe Ser Asn Asn Leu Leu Thr Asp Thr Val Phe Glu Asn Cys 335 340 345			1104
45	GGG CAC CTT ACT GAG TTG GAG ACA CTT ATT TTA CAA ATG AAT CAA TTA Gly His Leu Thr Glu Leu Glu Thr Leu Ile Leu Gln Met Asn Gln Leu 350 355 360			1152
50	AAA GAA CTT TCA AAA ATA GCT GAA ATG ACT ACA CAG ATG AAG TCT CTG Lys Glu Leu Ser Lys Ile Ala Glu Met Thr Thr Gln Met Lys Ser Leu 365 370 375			1200
55	CAA CAA TTG GAT ATT AGC CAG AAT TCT GTA AGC TAT GAT GAA AAG AAA Gln Gln Leu Asp Ile Ser Gln Asn Ser Val Ser Tyr Asp Glu Lys Lys 380 385 390			1248
60	GGA GAC TGT TCT TGG ACT AAA AGT TTA TTA AGT TTA AAT ATG TCT TCA Gly Asp Cys Ser Trp Thr Lys Ser Leu Leu Ser Leu Asn Met Ser Ser 395 400 405 410			1296
65	AAT ATA CTT ACT GAC ACT ATT TTC AGA TGT TTA CCT CCC AGG ATC AAG Asn Ile Leu Thr Asp Thr Ile Phe Arg Cys Leu Pro Pro Arg Ile Lys 415 420 425			1344
70	GTA CTT GAT CTT CAC AGC AAT AAA ATA AAG AGC ATT CCT AAA CAA GTC Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser Ile Pro Lys Gln Val 430 435 440			1392
75	GTA AAA CTG GAA GCT TTG CAA GAA CTC AAT GTT GCT TTC AAT TCT TTA Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val Ala Phe Asn Ser Leu 445 450 455			1440

5	ACT	GAC	CTT	CCT	GGA	TGT	GGC	AGC	TTT	AGC	AGC	CTT	TCT	GTA	TTG	ATC	1488
	Thr	Asp	Leu	Pro	Gly	Cys	Gly	Ser	Phe	Ser	Ser	Leu	Ser	Val	Leu	Ile	
	460						465					470					
10	ATT	GAT	CAC	AAT	TCA	GTT	TCC	CAC	CCA	TCA	GCT	GAT	TTC	TTC	CAG	AGC	1536
	Ile	Asp	His	Asn	Ser	Val	Ser	His	Pro	Ser	Ala	Asp	Phe	Phe	Gln	Ser	
	475					480					485					490	
15	TGC	CAG	AAG	ATG	AGG	TCA	ATA	AAA	GCA	GGG	GAC	AAT	CCA	TTC	CAA	TGT	1584
	Cys	Gln	Lys	Met	Arg	Ser	Ile	Lys	Ala	Gly	Asp	Asn	Pro	Phe	Gln	Cys	
					495					500					505		
20	ACC	TGT	GAG	CTC	GGA	GAA	TTT	GTC	AAA	AAT	ATA	GAC	CAA	GTA	TCA	AGT	1632
	Thr	Cys	Glu	Leu	Gly	Glu	Phe	Val	Lys	Asn	Ile	Asp	Gln	Val	Ser	Ser	
				510					515					520			
25	GAA	GTG	TTA	GAG	GGC	TGG	CCT	GAT	TCT	TAT	AAG	TGT	GAC	TAC	CCG	GAA	1680
	Glu	Val	Leu	Glu	Gly	Trp	Pro	Asp	Ser	Tyr	Lys	Cys	Asp	Tyr	Pro	Glu	
			525					530					535				
30	AGT	TAT	AGA	GGA	ACC	CTA	CTA	AAG	GAC	TTT	CAC	ATG	TCT	GAA	TTA	TCC	1728
	Ser	Tyr	Arg	Gly	Thr	Leu	Leu	Lys	Asp	Phe	His	Met	Ser	Glu	Leu	Ser	
		540					545					550					
35	TGC	AAC	ATA	ACT	CTG	CTG	ATC	GTC	ACC	ATC	GTT	GCC	ACC	ATG	CTG	GTG	1776
	Cys	Asn	Ile	Thr	Leu	Leu	Ile	Val	Thr	Ile	Val	Ala	Thr	Met	Leu	Val	
	555					560					565					570	
40	TTG	GCT	GTG	ACT	GTG	ACC	TCC	CTC	TGC	ATC	TAC	TTG	GAT	CTG	CCC	TGG	1824
	Leu	Ala	Val	Thr	Val	Thr	Ser	Leu	Cys	Ile	Tyr	Leu	Asp	Leu	Pro	Trp	
					575					580					585		
45	TAT	CTC	AGG	ATG	GTG	TGC	CAG	TGG	ACC	CAG	ACC	CGG	CGC	AGG	GCC	AGG	1872
	Tyr	Leu	Arg	Met	Val	Cys	Gln	Trp	Thr	Gln	Thr	Arg	Arg	Arg	Ala	Arg	
				590					595					600			
50	AAC	ATA	CCC	TTA	GAA	GAA	CTC	CAA	AGA	AAT	CTC	CAG	TTT	CAT	GCA	TTT	1920
	Asn	Ile	Pro	Leu	Glu	Glu	Leu	Gln	Arg	Asn	Leu	Gln	Phe	His	Ala	Phe	
			605					610					615				
55	ATT	TCA	TAT	AGT	GGG	CAC	GAT	TCT	TTC	TGG	GTG	AAG	AAT	GAA	TTA	TTG	1968
	Ile	Ser	Tyr	Ser	Gly	His	Asp	Ser	Phe	Trp	Val	Lys	Asn	Glu	Leu	Leu	
		620					625					630					
60	CCA	AAC	CTA	GAG	AAA	GAA	GGT	ATG	CAG	ATT	TGC	CTT	CAT	GAG	AGA	AAC	2016
	Pro	Asn	Leu	Glu	Lys	Glu	Gly	Met	Gln	Ile	Cys	Leu	His	Glu	Arg	Asn	
	635					640					645					650	
65	TTT	GTT	CCT	GGC	AAG	AGC	ATT	GTG	GAA	AAT	ATC	ATC	ACC	TGC	ATT	GAG	2064
	Phe	Val	Pro	Gly	Lys	Ser	Ile	Val	Glu	Asn	Ile	Ile	Thr	Cys	Ile	Glu	
					655					660					665		
70	AAG	AGT	TAC	AAG	TCC	ATC	TTT	GTT	TTG	TCT	CCC	AAC	TTT	GTC	CAG	AGT	2112
	Lys	Ser	Tyr	Lys	Ser	Ile	Phe	Val	Leu	Ser	Pro	Asn	Phe	Val	Gln	Ser	
				670						675				680			
75	GAA	TGG	TGC	CAT	TAT	GAA	CTC	TAC	TTT	GCC	CAT	CAC	AAT	CTC	TTT	CAT	2160
	Glu	Trp	Cys	His	Tyr	Glu	Leu	Tyr	Phe	Ala	His	His	Asn	Leu	Phe	His	
			685					690					695				

	GAA GGA TCT AAT AGC TTA ATC CTG ATC TTG CTG GAA CCC ATT CCG CAG	2208
	Glu Gly Ser Asn Ser Leu Ile Leu Ile Leu Leu Glu Pro Ile Pro Gln	
	700 705 710	
5	TAC TCC ATT CCT AGC AGT TAT CAC AAG CTC AAA AGT CTC ATG GCC AGG	2256
	Tyr Ser Ile Pro Ser Ser Tyr His Lys Leu Lys Ser Leu Met Ala Arg	
	715 720 725 730	
10	AGG ACT TAT TTG GAA TGG CCC AAG GAA AAG AGC AAA CGT GGC CTT TTT	2304
	Arg Thr Tyr Leu Glu Trp Pro Lys Glu Lys Ser Lys Arg Gly Leu Phe	
	735 740 745	
15	TGG GCT AAC TTA AGG GCA GCC ATT AAT ATT AAG CTG ACA GAG CAA GCA	2352
	Trp Ala Asn Leu Arg Ala Ala Ile Asn Ile Lys Leu Thr Glu Gln Ala	
	750 755 760	
	AAG AAA TAGTCTAGA	2367
	Lys Lys	
20		
	(2) INFORMATION FOR SEQ ID NO:2:	
	(i) SEQUENCE CHARACTERISTICS:	
25	(A) LENGTH: 786 amino acids	
	(B) TYPE: amino acid	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: protein	
30		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:	
	Met Thr Ser Ile Phe His Phe Ala Ile Ile Phe Met Leu Ile Leu Gln	
35	-22 -20 -15 -10	
	Ile Arg Ile Gln Leu Ser Glu Glu Ser Glu Phe Leu Val Asp Arg Ser	
	-5 1 5 10	
40	Lys Asn Gly Leu Ile His Val Pro Lys Asp Leu Ser Gln Lys Thr Thr	
	15 20 25	
	Ile Leu Asn Ile Ser Gln Asn Tyr Ile Ser Glu Leu Trp Thr Ser Asp	
	30 35 40	
45	Ile Leu Ser Leu Ser Lys Leu Arg Ile Leu Ile Ile Ser His Asn Arg	
	45 50 55	
	Ile Gln Tyr Leu Asp Ile Ser Val Phe Lys Phe Asn Gln Glu Leu Glu	
50	60 65 70	
	Tyr Leu Asp Leu Ser His Asn Lys Leu Val Lys Ile Ser Cys His Pro	
	75 80 85 90	
55	Thr Val Asn Leu Lys His Leu Asp Leu Ser Phe Asn Ala Phe Asp Ala	
	95 100 105	
	Leu Pro Ile Cys Lys Glu Phe Gly Asn Met Ser Gln Leu Lys Phe Leu	
	110 115 120	
60	Gly Leu Ser Thr Thr His Leu Glu Lys Ser Ser Val Leu Pro Ile Ala	
	125 130 135	

	His	Leu	Asn	Ile	Ser	Lys	Val	Leu	Leu	Val	Leu	Gly	Glu	Thr	Tyr	Gly	
	140						145					150					
5	Glu	Lys	Glu	Asp	Pro	Glu	Gly	Leu	Gln	Asp	Phe	Asn	Thr	Glu	Ser	Leu	
	155					160					165					170	
	His	Ile	Val	Phe	Pro	Thr	Asn	Lys	Glu	Phe	His	Phe	Ile	Leu	Asp	Val	
					175					180					185		
10	Ser	Val	Lys	Thr	Val	Ala	Asn	Leu	Glu	Leu	Ser	Asn	Ile	Lys	Cys	Val	
				190					195					200			
	Leu	Glu	Asp	Asn	Lys	Cys	Ser	Tyr	Phe	Leu	Ser	Ile	Leu	Ala	Lys	Leu	
15			205					210					215				
	Gln	Thr	Asn	Pro	Lys	Leu	Ser	Ser	Leu	Thr	Leu	Asn	Asn	Ile	Glu	Thr	
		220					225					230					
20	Thr	Trp	Asn	Ser	Phe	Ile	Arg	Ile	Leu	Gln	Leu	Val	Trp	His	Thr	Thr	
	235					240					245					250	
	Val	Trp	Tyr	Phe	Ser	Ile	Ser	Asn	Val	Lys	Leu	Gln	Gly	Gln	Leu	Asp	
					255					260					265		
25	Phe	Arg	Asp	Phe	Asp	Tyr	Ser	Gly	Thr	Ser	Leu	Lys	Ala	Leu	Ser	Ile	
				270				275						280			
	His	Gln	Val	Val	Ser	Asp	Val	Phe	Gly	Phe	Pro	Gln	Ser	Tyr	Ile	Tyr	
30			285					290					295				
	Glu	Ile	Phe	Ser	Asn	Met	Asn	Ile	Lys	Asn	Phe	Thr	Val	Ser	Gly	Thr	
	300						305					310					
35	Arg	Met	Val	His	Met	Leu	Cys	Pro	Ser	Lys	Ile	Ser	Pro	Phe	Leu	His	
	315					320					325					330	
	Leu	Asp	Phe	Ser	Asn	Asn	Leu	Leu	Thr	Asp	Thr	Val	Phe	Glu	Asn	Cys	
					335					340					345		
40	Gly	His	Leu	Thr	Glu	Leu	Glu	Thr	Leu	Ile	Leu	Gln	Met	Asn	Gln	Leu	
				350					355					360			
	Lys	Glu	Leu	Ser	Lys	Ile	Ala	Glu	Met	Thr	Thr	Gln	Met	Lys	Ser	Leu	
45			365					370					375				
	Gln	Gln	Leu	Asp	Ile	Ser	Gln	Asn	Ser	Val	Ser	Tyr	Asp	Glu	Lys	Lys	
		380					385					390					
50	Gly	Asp	Cys	Ser	Trp	Thr	Lys	Ser	Leu	Leu	Ser	Leu	Asn	Met	Ser	Ser	
	395					400					405					410	
	Asn	Ile	Leu	Thr	Asp	Thr	Ile	Phe	Arg	Cys	Leu	Pro	Pro	Arg	Ile	Lys	
					415					420					425		
55	Val	Leu	Asp	Leu	His	Ser	Asn	Lys	Ile	Lys	Ser	Ile	Pro	Lys	Gln	Val	
				430					435					440			
	Val	Lys	Leu	Glu	Ala	Leu	Gln	Glu	Leu	Asn	Val	Ala	Phe	Asn	Ser	Leu	
60			445					450					455				

Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser Leu Ser Val Leu Ile  
 460 465 470  
 5 Ile Asp His Asn Ser Val Ser His Pro Ser Ala Asp Phe Phe Gln Ser  
 475 480 485 490  
 Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp Asn Pro Phe Gln Cys  
 495 500 505  
 10 Thr Cys Glu Leu Gly Glu Phe Val Lys Asn Ile Asp Gln Val Ser Ser.  
 510 515 520  
 Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys Cys Asp Tyr Pro Glu  
 525 530 535  
 15 Ser Tyr Arg Gly Thr Leu Leu Lys Asp Phe His Met Ser Glu Leu Ser  
 540 545 550  
 20 Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Val Ala Thr Met Leu Val  
 555 560 565 570  
 Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr Leu Asp Leu Pro Trp  
 575 580 585  
 25 Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr Arg Arg Arg Ala Arg  
 590 595 600  
 Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe  
 605 610 615  
 30 Ile Ser Tyr Ser Gly His Asp Ser Phe Trp Val Lys Asn Glu Leu Leu  
 620 625 630  
 35 Pro Asn Leu Glu Lys Glu Gly Met Gln Ile Cys Leu His Glu Arg Asn  
 635 640 645 650  
 Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Thr Cys Ile Glu  
 655 660 665  
 40 Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Ser  
 670 675 680  
 Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His  
 685 690 695  
 45 Glu Gly Ser Asn Ser Leu Ile Leu Ile Leu Leu Glu Pro Ile Pro Gln  
 700 705 710  
 50 Tyr Ser Ile Pro Ser Ser Tyr His Lys Leu Lys Ser Leu Met Ala Arg  
 715 720 725 730  
 Arg Thr Tyr Leu Glu Trp Pro Lys Glu Lys Ser Lys Arg Gly Leu Phe  
 735 740 745  
 55 Trp Ala Asn Leu Arg Ala Ala Ile Asn Ile Lys Leu Thr Glu Gln Ala  
 750 755 760  
 Lys Lys

60

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 2355 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..2352

(ix) FEATURE:  
 (A) NAME/KEY: mat\_peptide  
 (B) LOCATION: 67..2352

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

5	ATG CCA CAT ACT TTG TGG ATG GTG TGG GTC TTG GGG GTC ATC ATC AGC	48
	Met Pro His Thr Leu Trp Met Val Trp Val Leu Gly Val Ile Ile Ser	
	-22 -20 -15 -10	
25	CTC TCC AAG GAA GAA TCC TCC AAT CAG GCT TCT CTG TCT TGT GAC CGC	96
	Leu Ser Lys Glu Glu Ser Ser Asn Gln Ala Ser Leu Ser Cys Asp Arg	
	-5 1 5 10	
30	AAT GGT ATC TGC AAG GGC AGC TCA GGA TCT TTA AAC TCC ATT CCC TCA	144
	Asn Gly Ile Cys Lys Gly Ser Ser Gly Ser Leu Asn Ser Ile Pro Ser	
	15 20 25	
35	GGG CTC ACA GAA GCT GTA AAA AGC CTT GAC CTG TCC AAC AAC AGG ATC	192
	Gly Leu Thr Glu Ala Val Lys Ser Leu Asp Leu Ser Asn Asn Arg Ile	
	30 35 40	
40	ACC TAC ATT AGC AAC AGT GAC CTA CAG AGG TGT GTG AAC CTC CAG GCT	240
	Thr Tyr Ile Ser Asn Ser Asp Leu Gln Arg Cys Val Asn Leu Gln Ala	
	45 50 55	
45	CTG GTG CTG ACA TCC AAT GGA ATT AAC ACA ATA GAG GAA GAT TCT TTT	288
	Leu Val Leu Thr Ser Asn Gly Ile Asn Thr Ile Glu Glu Asp Ser Phe	
	60 65 70	
50	TCT TCC CTG GGC AGT CTT GAA CAT TTA GAC TTA TCC TAT AAT TAC TTA	336
	Ser Ser Leu Gly Ser Leu Glu His Leu Asp Leu Ser Tyr Asn Tyr Leu	
	75 80 85 90	
55	TCT AAT TTA TCG TCT TCC TGG TTC AAG CCC CTT TCT TCT TTA ACA TTC	384
	Ser Asn Leu Ser Ser Ser Trp Phe Lys Pro Leu Ser Ser Leu Thr Phe	
	95 100 105	
60	TTA AAC TTA CTG GGA AAT CCT TAC AAA ACC CTA GGG GAA ACA TCT CTT	432
	Leu Asn Leu Leu Gly Asn Pro Tyr Lys Thr Leu Gly Glu Thr Ser Leu	
	110 115 120	
60	TTT TCT CAT CTC ACA AAA TTG CAA ATC CTG AGA GTG GGA AAT ATG GAC	480
	Phe Ser His Leu Thr Lys Leu Gln Ile Leu Arg Val Gly Asn Met Asp	
	125 130 135	



	ACC	TTC	ACT	AAG	ATT	CAA	AGA	AAA	GAT	TTT	GCT	GGA	CTT	ACC	TTC	CTT	528
	Thr	Phe	Thr	Lys	Ile	Gln	Arg	Lys	Asp	Phe	Ala	Gly	Leu	Thr	Phe	Leu	
	140						145					150					
5	GAG	GAA	CTT	GAG	ATT	GAT	GCT	TCA	GAT	CTA	CAG	AGC	TAT	GAG	CCA	AAA	576
	Glu	Glu	Leu	Glu	Ile	Asp	Ala	Ser	Asp	Leu	Gln	Ser	Tyr	Glu	Pro	Lys	
	155					160					165					170	
10	AGT	TTG	AAG	TCA	ATT	CAG	AAC	GTA	AGT	CAT	CTG	ATC	CTT	CAT	ATG	AAG	624
	Ser	Leu	Lys	Ser	Ile	Gln	Asn	Val	Ser	His	Leu	Ile	Leu	His	Met	Lys	
					175					180					185		
15	CAG	CAT	ATT	TTA	CTG	CTG	GAG	ATT	TTT	GTA	GAT	GTT	ACA	AGT	TCC	GTG	672
	Gln	His	Ile	Leu	Leu	Leu	Glu	Ile	Phe	Val	Asp	Val	Thr	Ser	Ser	Val	
				190					195					200			
20	GAA	TGT	TTG	GAA	CTG	CGA	GAT	ACT	GAT	TTG	GAC	ACT	TTC	CAT	TTT	TCA	720
	Glu	Cys	Leu	Glu	Leu	Arg	Asp	Thr	Asp	Leu	Asp	Thr	Phe	His	Phe	Ser	
			205					210					215				
25	GAA	CTA	TCC	ACT	GGT	GAA	ACA	AAT	TCA	TTG	ATT	AAA	AAG	TTT	ACA	TTT	768
	Glu	Leu	Ser	Thr	Gly	Glu	Thr	Asn	Ser	Leu	Ile	Lys	Lys	Phe	Thr	Phe	
		220					225					230					
30	AGA	AAT	GTG	AAA	ATC	ACC	GAT	GAA	AGT	TTG	TTT	CAG	GTT	ATG	AAA	CTT	816
	Arg	Asn	Val	Lys	Ile	Thr	Asp	Glu	Ser	Leu	Phe	Gln	Val	Met	Lys	Leu	
	235					240					245					250	
35	TTG	AAT	CAG	ATT	TCT	GGA	TTG	TTA	GAA	TTA	GAG	TTT	GAT	GAC	TGT	ACC	864
	Leu	Asn	Gln	Ile	Ser	Gly	Leu	Leu	Glu	Leu	Glu	Phe	Asp	Asp	Cys	Thr	
					255					260					265		
40	CTT	AAT	GGA	GTT	GGT	AAT	TTT	AGA	GCA	TCT	GAT	AAT	GAC	AGA	GTT	ATA	912
	Leu	Asn	Gly	Val	Gly	Asn	Phe	Arg	Ala	Ser	Asp	Asn	Asp	Arg	Val	Ile	
				270				275						280			
45	GAT	CCA	GGT	AAA	GTG	GAA	ACG	TTA	ACA	ATC	CGG	AGG	CTG	CAT	ATT	CCA	960
	Asp	Pro	Gly	Lys	Val	Glu	Thr	Leu	Thr	Ile	Arg	Arg	Leu	His	Ile	Pro	
			285					290					295				
50	AGG	TTT	TAC	TTA	TTT	TAT	GAT	CTG	AGC	ACT	TTA	TAT	TCA	CTT	ACA	GAA	1008
	Arg	Phe	Tyr	Leu	Phe	Tyr	Asp	Leu	Ser	Thr	Leu	Tyr	Ser	Leu	Thr	Glu	
		300					305					310					
55	AGA	GTT	AAA	AGA	ATC	ACA	GTA	GAA	AAC	AGT	AAA	GTT	TTT	CTG	GTT	CCT	1056
	Arg	Val	Lys	Arg	Ile	Thr	Val	Glu	Asn	Ser	Lys	Val	Phe	Leu	Val	Pro	
	315					320					325					330	
60	TGT	TTA	CTT	TCA	CAA	CAT	TTA	AAA	TCA	TTA	GAA	TAC	TTG	GAT	CTC	AGT	1104
	Cys	Leu	Leu	Ser	Gln	His	Leu	Lys	Ser	Leu	Glu	Tyr	Leu	Asp	Leu	Ser	
					335					340					345		
65	GAA	AAT	TTG	ATG	GTT	GAA	GAA	TAC	TTG	AAA	AAT	TCA	GCC	TGT	GAG	GAT	1152
	Glu	Asn	Leu	Met	Val	Glu	Glu	Tyr	Leu	Lys	Asn	Ser	Ala	Cys	Glu	Asp	
				350				355						360			
70	GCC	TGG	CCC	TCT	CTA	CAA	ACT	TTA	ATT	TTA	AGG	CAA	AAT	CAT	TTG	GCA	1200
	Ala	Trp	Pro	Ser	Leu	Gln	Thr	Leu	Ile	Leu	Arg	Gln	Asn	His	Leu	Ala	
			365				370						375				
75	TCA	TTG	GAA	AAA	ACC	GGA	GAG	ACT	TTG	CTC	ACT	CTG	AAA	AAC	TTG	ACT	1248

	Ser	Leu	Glu	Lys	Thr	Gly	Glu	Thr	Leu	Leu	Thr	Leu	Lys	Asn	Leu	Thr	
	380						385					390					
5	AAC	ATT	GAT	ATC	AGT	AAG	AAT	AGT	TTT	CAT	TCT	ATG	CCT	GAA	ACT	TGT	1296
	Asn	Ile	Asp	Ile	Ser	Lys	Asn	Ser	Phe	His	Ser	Met	Pro	Glu	Thr	Cys	
	395					400					405					410	
10	CAG	TGG	CCA	GAA	AAG	ATG	AAA	TAT	TTG	AAC	TTA	TCC	AGC	ACA	CGA	ATA	1344
	Gln	Trp	Pro	Glu	Lys	Met	Lys	Tyr	Leu	Asn	Leu	Ser	Ser	Thr	Arg	Ile	
					415					420					425		
15	CAC	AGT	GTA	ACA	GGC	TGC	ATT	CCC	AAG	ACA	CTG	GAA	ATT	TTA	GAT	GTT	1392
	His	Ser	Val	Thr	Gly	Cys	Ile	Pro	Lys	Thr	Leu	Glu	Ile	Leu	Asp	Val	
				430					435					440			
20	AGC	AAC	AAC	AAT	CTC	AAT	TTA	TTT	TCT	TTG	AAT	TTG	CCG	CAA	CTC	AAA	1440
	Ser	Asn	Asn	Asn	Leu	Asn	Leu	Phe	Ser	Leu	Asn	Leu	Pro	Gln	Leu	Lys	
				445				450					455				
25	GAA	CTT	TAT	ATT	TCC	AGA	AAT	AAG	TTG	ATG	ACT	CTA	CCA	GAT	GCC	TCC	1488
	Glu	Leu	Tyr	Ile	Ser	Arg	Asn	Lys	Leu	Met	Thr	Leu	Pro	Asp	Ala	Ser	
		460					465					470					
30	CTC	TTA	CCC	ATG	TTA	CTA	GTA	TTG	AAA	ATC	AGT	AGG	AAT	GCA	ATA	ACT	1536
	Leu	Leu	Pro	Met	Leu	Leu	Val	Leu	Lys	Ile	Ser	Arg	Asn	Ala	Ile	Thr	
	475					480					485					490	
35	ACG	TTT	TCT	AAG	GAG	CAA	CTT	GAC	TCA	TTT	CAC	ACA	CTG	AAG	ACT	TTG	1584
	Thr	Phe	Ser	Lys	Glu	Gln	Leu	Asp	Ser	Phe	His	Thr	Leu	Lys	Thr	Leu	
				495						500					505		
40	GAA	GCT	GGT	GGC	AAT	AAC	TTC	ATT	TGC	TCC	TGT	GAA	TTC	CTC	TCC	TTC	1632
	Glu	Ala	Gly	Gly	Asn	Asn	Phe	Ile	Cys	Ser	Cys	Glu	Phe	Leu	Ser	Phe	
				510					515					520			
45	ACT	CAG	GAG	CAG	CAA	GCA	CTG	GCC	AAA	GTC	TTG	ATT	GAT	TGG	CCA	GCA	1680
	Thr	Gln	Glu	Gln	Gln	Ala	Leu	Ala	Lys	Val	Leu	Ile	Asp	Trp	Pro	Ala	
				525				530					535				
50	AAT	TAC	CTG	TGT	GAC	TCT	CCA	TCC	CAT	GTG	CGT	GGC	CAG	CAG	GTT	CAG	1728
	Asn	Tyr	Leu	Cys	Asp	Ser	Pro	Ser	His	Val	Arg	Gly	Gln	Gln	Val	Gln	
		540					545					550					
55	GAT	GTC	CGC	CTC	TCG	GTG	TCG	GAA	TGT	CAC	AGG	ACA	GCA	CTG	GTG	TCT	1776
	Asp	Val	Arg	Leu	Ser	Val	Ser	Glu	Cys	His	Arg	Thr	Ala	Leu	Val	Ser	
	555					560					565					570	
60	GGC	ATG	TGC	TGT	GCT	CTG	TTC	CTG	CTG	ATC	CTG	CTC	ACG	GGG	GTC	CTG	1824
	Gly	Met	Cys	Cys	Ala	Leu	Phe	Leu	Leu	Ile	Leu	Leu	Thr	Gly	Val	Leu	
					575					580					585		
65	TGC	CAC	CGT	TTC	CAT	GGC	CTG	TGG	TAT	ATG	AAA	ATG	ATG	TGG	GCC	TGG	1872
	Cys	His	Arg	Phe	His	Gly	Leu	Trp	Tyr	Met	Lys	Met	Met	Trp	Ala	Trp	
				590					595					600			
70	CTC	CAG	GCC	AAA	AGG	AAG	CCC	AGG	AAA	GCT	CCC	AGC	AGG	AAC	ATC	TGC	1920
	Leu	Gln	Ala	Lys	Arg	Lys	Pro	Arg	Lys	Ala	Pro	Ser	Arg	Asn	Ile	Cys	
			605					610					615				
75	TAT	GAT	GCA	TTT	GTT	TCT	TAC	AGT	GAG	CGG	GAT	GCC	TAC	TGG	GTG	GAG	1968
	Tyr	Asp	Ala	Phe	Val	Ser	Tyr	Ser	Glu	Arg	Asp	Ala	Tyr	Trp	Val	Glu	



	45	50	55
	Leu Val 60	Leu Thr Ser Asn Gly 65	Ile Asn Thr Ile Glu 70
5	Ser 75	Ser Leu Gly 80	Leu Asp Leu Ser Tyr Asn Tyr Leu 90
10	Ser Asn Leu Ser 95	Ser Trp Phe Lys 100	Pro Leu Ser Ser Leu Thr Phe 105
	Leu Asn Leu 110	Leu Gly Asn Pro Tyr Lys 115	Thr Leu Gly Glu Thr Ser Leu 120
15	Phe Ser His 125	Leu Thr Lys Leu Gln 130	Ile Leu Arg Val Gly Asn Met Asp 135
20	Thr Phe Thr 140	Lys Ile Gln Arg Lys 145	Asp Phe Ala Gly Leu Thr Phe Leu 150
	Glu Glu Leu 155	Glu Ile Asp Ala Ser 160	Asp Leu Gln Ser Tyr Glu Pro Lys 170
25	Ser Leu Lys Ser 175	Ile Gln Asn Val Ser 180	His Leu Ile Leu His Met Lys 185
	Gln His Ile 190	Leu Leu Leu Glu Ile Phe 195	Val Asp Val Thr Ser Ser Val 200
30	Glu Cys Leu 205	Glu Leu Arg Asp Thr 210	Asp Leu Asp Thr Phe His Phe Ser 215
35	Glu Leu Ser 220	Thr Gly Glu Thr Asn Ser 225	Leu Ile Lys Lys Phe Thr Phe 230
	Arg Asn Val 235	Lys Ile Thr Asp Glu Ser 240	Leu Phe Gln Val Met Lys Leu 250
40	Leu Asn Gln 255	Ile Ser Gly Leu Leu Glu 260	Leu Glu Phe Asp Asp Cys Thr 265
	Leu Asn Gly 270	Val Gly Asn Phe Arg Ala 275	Ser Asp Asn Asp Arg Val Ile 280
45	Asp Pro Gly 285	Lys Val Glu Thr Leu Thr 290	Ile Arg Arg Leu His Ile Pro 295
50	Arg Phe Tyr 300	Leu Phe Tyr Asp Leu Ser 305	Thr Leu Tyr Ser Leu Thr Glu 310
	Arg Val Lys 315	Arg Ile Thr Val Glu Asn Ser 320	Lys Val Phe Leu Val Pro 330
55	Cys Leu Leu 335	Ser Gln His Leu Lys Ser 340	Leu Glu Tyr Leu Asp Leu Ser 345
	Glu Asn Leu 350	Met Val Glu Glu Tyr Leu Lys 355	Asn Ser Ala Cys Glu Asp 360
60	Ala Trp Pro 365	Ser Leu Gln Thr Leu Ile 370	Leu Arg Gln Asn His Leu Ala 375

Ser Leu Glu Lys Thr Gly Glu Thr Leu Leu Thr Leu Lys Asn Leu Thr  
 380 385 390  
 5 Asn Ile Asp Ile Ser Lys Asn Ser Phe His Ser Met Pro Glu Thr Cys  
 395 400 405 410  
 Gln Trp Pro Glu Lys Met Lys Tyr Leu Asn Leu Ser Ser Thr Arg Ile  
 415 420 425  
 10 His Ser Val Thr Gly Cys Ile Pro Lys Thr Leu Glu Ile Leu Asp Val  
 430 435 440  
 Ser Asn Asn Asn Leu Asn Leu Phe Ser Leu Asn Leu Pro Gln Leu Lys  
 445 450 455  
 15 Glu Leu Tyr Ile Ser Arg Asn Lys Leu Met Thr Leu Pro Asp Ala Ser  
 460 465 470  
 20 Leu Leu Pro Met Leu Leu Val Leu Lys Ile Ser Arg Asn Ala Ile Thr  
 475 480 485 490  
 Thr Phe Ser Lys Glu Gln Leu Asp Ser Phe His Thr Leu Lys Thr Leu  
 495 500 505  
 25 Glu Ala Gly Gly Asn Asn Phe Ile Cys Ser Cys Glu Phe Leu Ser Phe  
 510 515 520  
 Thr Gln Glu Gln Gln Ala Leu Ala Lys Val Leu Ile Asp Trp Pro Ala  
 525 530 535  
 30 Asn Tyr Leu Cys Asp Ser Pro Ser His Val Arg Gly Gln Gln Val Gln  
 540 545 550  
 35 Asp Val Arg Leu Ser Val Ser Glu Cys His Arg Thr Ala Leu Val Ser  
 555 560 565 570  
 Gly Met Cys Cys Ala Leu Phe Leu Leu Ile Leu Leu Thr Gly Val Leu  
 575 580 585  
 40 Cys His Arg Phe His Gly Leu Trp Tyr Met Lys Met Met Trp Ala Trp  
 590 595 600  
 Leu Gln Ala Lys Arg Lys Pro Arg Lys Ala Pro Ser Arg Asn Ile Cys  
 605 610 615  
 45 Tyr Asp Ala Phe Val Ser Tyr Ser Glu Arg Asp Ala Tyr Trp Val Glu  
 620 625 630  
 50 Asn Leu Met Val Gln Glu Leu Glu Asn Phe Asn Pro Pro Phe Lys Leu  
 635 640 645 650  
 Cys Leu His Lys Arg Asp Phe Ile Pro Gly Lys Trp Ile Ile Asp Asn  
 655 660 665  
 55 Ile Ile Asp Ser Ile Glu Lys Ser His Lys Thr Val Phe Val Leu Ser  
 670 675 680  
 60 Glu Asn Phe Val Lys Ser Glu Trp Cys Lys Tyr Glu Leu Asp Phe Ser  
 685 690 695

His Phe Arg Leu Phe Glu Glu Asn Asn Asp Ala Ala Ile Leu Ile Leu  
 700 705 710  
 5 Leu Glu Pro Ile Glu Lys Lys Ala Ile Pro Gln Arg Phe Cys Lys Leu  
 715 720 725 730  
 Arg Lys Ile Met Asn Thr Lys Thr Tyr Leu Glu Trp Pro Met Asp Glu  
 735 740 745  
 10 Ala Gln Arg Glu Gly Phe Trp Val Asn Leu Arg Ala Ala Ile Lys Ser  
 750 755 760

## (2) INFORMATION FOR SEQ ID NO:5:

15

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 2715 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

25

- (ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..2712

30

- (ix) FEATURE:  
 (A) NAME/KEY: mat\_peptide  
 (B) LOCATION: 64..2712

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ATG AGA CAG ACT TTG CCT TGT ATC TAC TTT TGG GGG GGC CTT TTG CCC 48  
 Met Arg Gln Thr Leu Pro Cys Ile Tyr Phe Trp Gly Gly Leu Leu Pro  
 -21 -20 -15 -10  
 40 TTT GGG ATG CTG TGT GCA TCC TCC ACC ACC AAG TGC ACT GTT AGC CAT 96  
 Phe Gly Met Leu Cys Ala Ser Ser Thr Thr Lys Cys Thr Val Ser His  
 -5 1 5 10  
 45 GAA GTT GCT GAC TGC AGC CAC CTG AAG TTG ACT CAG GTA CCC GAT GAT 144  
 Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp  
 15 20 25  
 50 CTA CCC ACA AAC ATA ACA GTG TTG AAC CTT ACC CAT AAT CAA CTC AGA 192  
 Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg  
 30 35 40  
 AGA TTA CCA GCC GCC AAC TTC ACA AGG TAT AGC CAG CTA ACT AGC TTG 240  
 Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu  
 45 50 55  
 55 GAT GTA GGA TTT AAC ACC ATC TCA AAA CTG GAG CCA GAA TTG TGC CAG 288  
 Asp Val Gly Phe Asn Thr Ile Ser Lys Leu Glu Pro Glu Leu Cys Gln  
 60 65 70 75  
 60 AAA CTT CCC ATG TTA AAA GTT TTG AAC CTC CAG CAC AAT GAG CTA TCT 336  
 Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser



5	TGG CTA AAA TGT TTG GAG CAC CTT AAC ATG GAA GAT AAT GAT ATT CCA Trp Leu Lys Cys Leu Glu His Leu Asn Met Glu Asp Asn Asp Ile Pro 335 340 345	1104
10	GGC ATA AAA AGC AAT ATG TTC ACA GGA TTG ATA AAC CTG AAA TAC TTA Gly Ile Lys Ser Asn Met Phe Thr Gly Leu Ile Asn Leu Lys Tyr Leu 350 355 360	1152
15	AGT CTA TCC AAC TCC TTT ACA AGT TTG CGA ACT TTG ACA AAT GAA ACA Ser Leu Ser Asn Ser Phe Thr Ser Leu Arg Thr Leu Thr Asn Glu Thr 365 370 375	1200
20	TTT GTA TCA CTT GCT CAT TCT CCC TTA CAC ATA CTC AAC CTA ACC AAG Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys 380 385 390 395	1248
25	AAT AAA ATC TCA AAA ATA GAG AGT GAT GCT TTC TCT TGG TTG GGC CAC Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His 400 405 410	1296
30	CTA GAA GTA CTT GAC CTG GGC CTT AAT GAA ATT GGG CAA GAA CTC ACA Leu Glu Val Leu Asp Leu Gly Leu Asn Glu Ile Gly Gln Glu Leu Thr 415 420 425	1344
35	GGC CAG GAA TGG AGA GGT CTA GAA AAT ATT TTC GAA ATC TAT CTT TCC Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser 430 435 440	1392
40	TAC AAC AAG TAC CTG CAG CTG ACT AGG AAC TCC TTT GCC TTG GTC CCA Tyr Asn Lys Tyr Leu Gln Leu Thr Arg Asn Ser Phe Ala Leu Val Pro 445 450 455	1440
45	AGC CTT CAA CGA CTG ATG CTC CGA AGG GTG GCC CTT AAA AAT GTG GAT Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val Asp 460 465 470 475	1488
50	AGC TCT CCT TCA CCA TTC CAG CCT CTT CGT AAC TTG ACC ATT CTG GAT Ser Ser Pro Ser Pro Phe Gln Pro Leu Arg Asn Leu Thr Ile Leu Asp 480 485 490	1536
55	CTA AGC AAC AAC AAC ATA GCC AAC ATA AAT GAT GAC ATG TTG GAG GGT Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Asp Asp Met Leu Glu Gly 495 500 505	1584
60	CTT GAG AAA CTA GAA ATT CTC GAT TTG CAG CAT AAC AAC TTA GCA CGG Leu Glu Lys Leu Glu Ile Leu Asp Leu Gln His Asn Asn Leu Ala Arg 510 515 520	1632
65	CTC TGG AAA CAC GCA AAC CCT GGT GGT CCC ATT TAT TTC CTA AAG GGT Leu Trp Lys His Ala Asn Pro Gly Gly Pro Ile Tyr Phe Leu Lys Gly 525 530 535	1680
70	CTG TCT CAC CTC CAC ATC CTT AAC TTG GAG TCC AAC GGC TTT GAC GAG Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu 540 545 550 555	1728
75	ATC CCA GTT GAG GTC TTC AAG GAT TTA TTT GAA CTA AAG ATC ATC GAT Ile Pro Val Glu Val Phe Lys Asp Leu Phe Glu Leu Lys Ile Ile Asp 560 565 570	1776



	TTA	GGA	TTG	AAT	AAT	TTA	AAC	ACA	CTT	CCA	GCA	TCT	GTC	TTT	AAT	AAT	1824
	Leu	Gly	Leu	Asn	Asn	Leu	Asn	Thr	Leu	Pro	Ala	Ser	Val	Phe	Asn	Asn	
				575					580					585			
5	CAG	GTG	TCT	CTA	AAG	TCA	TTG	AAC	CTT	CAG	AAG	AAT	CTC	ATA	ACA	TCC	1872
	Gln	Val	Ser	Leu	Lys	Ser	Leu	Asn	Leu	Gln	Lys	Asn	Leu	Ile	Thr	Ser	
			590					595					600				
10	GTT	GAG	AAG	AAG	GTT	TTC	GGG	CCA	GCT	TTC	AGG	AAC	CTG	ACT	GAG	TTA	1920
	Val	Glu	Lys	Lys	Val	Phe	Gly	Pro	Ala	Phe	Arg	Asn	Leu	Thr	Glu	Leu	
		605					610					615					
15	GAT	ATG	CGC	TTT	AAT	CCC	TTT	GAT	TGC	ACG	TGT	GAA	AGT	ATT	GCC	TGG	1968
	Asp	Met	Arg	Phe	Asn	Pro	Phe	Asp	Cys	Thr	Cys	Glu	Ser	Ile	Ala	Trp	
	620					625					630					635	
20	TTT	GTT	AAT	TGG	ATT	AAC	GAG	ACC	CAT	ACC	AAC	ATC	CCT	GAG	CTG	TCA	2016
	Phe	Val	Asn	Trp	Ile	Asn	Glu	Thr	His	Thr	Asn	Ile	Pro	Glu	Leu	Ser	
				640						645				650			
	AGC	CAC	TAC	CTT	TGC	AAC	ACT	CCA	CCT	CAC	TAT	CAT	GGG	TTC	CCA	GTG	2064
	Ser	His	Tyr	Leu	Cys	Asn	Thr	Pro	Pro	His	Tyr	His	Gly	Phe	Pro	Val	
				655				660					665				
25	AGA	CTT	TTT	GAT	ACA	TCA	TCT	TGC	AAA	GAC	AGT	GCC	CCC	TTT	GAA	CTC	2112
	Arg	Leu	Phe	Asp	Thr	Ser	Ser	Cys	Lys	Asp	Ser	Ala	Pro	Phe	Glu	Leu	
			670					675					680				
30	TTT	TTC	ATG	ATC	AAT	ACC	AGT	ATC	CTG	TTG	ATT	TTT	ATC	TTT	ATT	GTA	2160
	Phe	Phe	Met	Ile	Asn	Thr	Ser	Ile	Leu	Leu	Ile	Phe	Ile	Phe	Ile	Val	
		685					690					695					
35	CTT	CTC	ATC	CAC	TTT	GAG	GGC	TGG	AGG	ATA	TCT	TTT	TAT	TGG	AAT	GTT	2208
	Leu	Leu	Ile	His	Phe	Glu	Gly	Trp	Arg	Ile	Ser	Phe	Tyr	Trp	Asn	Val	
	700					705					710					715	
40	TCA	GTA	CAT	CGA	GTT	CTT	GGT	TTC	AAA	GAA	ATA	GAC	AGA	CAG	ACA	GAA	2256
	Ser	Val	His	Arg	Val	Leu	Gly	Phe	Lys	Glu	Ile	Asp	Arg	Gln	Thr	Glu	
				720						725					730		
	CAG	TTT	GAA	TAT	GCA	GCA	TAT	ATA	ATT	CAT	GCC	TAT	AAA	GAT	AAG	GAT	2304
	Gln	Phe	Glu	Tyr	Ala	Ala	Tyr	Ile	Ile	His	Ala	Tyr	Lys	Asp	Lys	Asp	
				735				740					745				
45	TGG	GTC	TGG	GAA	CAT	TTC	TCT	TCA	ATG	GAA	AAG	GAA	GAC	CAA	TCT	CTC	2352
	Trp	Val	Trp	Glu	His	Phe	Ser	Ser	Met	Glu	Lys	Glu	Asp	Gln	Ser	Leu	
			750					755					760				
50	AAA	TTT	TGT	CTG	GAA	GAA	AGG	GAC	TTT	GAG	GCG	GGT	GTT	TTT	GAA	CTA	2400
	Lys	Phe	Cys	Leu	Glu	Glu	Arg	Asp	Phe	Glu	Ala	Gly	Val	Phe	Glu	Leu	
		765					770					775					
55	GAA	GCA	ATT	GTT	AAC	AGC	ATC	AAA	AGA	AGC	AGA	AAA	ATT	ATT	TTT	GTT	2448
	Glu	Ala	Ile	Val	Asn	Ser	Ile	Lys	Arg	Ser	Arg	Lys	Ile	Ile	Phe	Val	
	780					785					790					795	
60	ATA	ACA	CAC	CAT	CTA	TTA	AAA	GAC	CCA	TTA	TGC	AAA	AGA	TTC	AAG	GTA	2496
	Ile	Thr	His	His	Leu	Leu	Lys	Asp	Pro	Leu	Cys	Lys	Arg	Phe	Lys	Val	
					800					805					810		
	CAT	CAT	GCA	GTT	CAA	CAA	GCT	ATT	GAA	CAA	AAT	CTG	GAT	TCC	ATT	ATA	2544

His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile  
 815 820 825  
 5 TTG GTT TTC CTT GAG GAG ATT CCA GAT TAT AAA CTG AAC CAT GCA CTC 2592  
 Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu  
 830 835 840  
 10 TGT TTG CGA AGA GGA ATG TTT AAA TCT CAC TGC ATC TTG AAC TGG CCA 2640  
 Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro  
 845 850 855  
 GTT CAG AAA GAA CGG ATA GGT GCC TTT CGT CAT AAA TTG CAA GTA GCA 2688  
 Val Gln Lys Glu Arg Ile Gly Ala Phe Arg His Lys Leu Gln Val Ala  
 860 865 870 875  
 15 CTT GGA TCC AAA AAC TCT GTA CAT TAA 2715  
 Leu Gly Ser Lys Asn Ser Val His  
 880  
 20  
 (2) INFORMATION FOR SEQ ID NO:6:  
 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 904 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: protein  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:  
 30 Met Arg Gln Thr Leu Pro Cys Ile Tyr Phe Trp Gly Gly Leu Leu Pro  
 -21 -20 -15 -10  
 35 Phe Gly Met Leu Cys Ala Ser Ser Thr Thr Lys Cys Thr Val Ser His  
 -5 1 5 10  
 Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp  
 15 20 25  
 40 Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg  
 30 35 40  
 Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu  
 45 45 50 55  
 Asp Val Gly Phe Asn Thr Ile Ser Lys Leu Glu Pro Glu Leu Cys Gln  
 60 65 70 75  
 50 Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser  
 80 85 90  
 Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu  
 95 100 105  
 55 His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val  
 110 115 120  
 Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser  
 60 125 130 135

Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu  
 140 145 150 155  
 5 Leu Leu Ser Asn Asn Lys Ile Gln Ala Leu Lys Ser Glu Glu Leu Asp  
 160 165 170  
 Ile Phe Ala Asn Ser Ser Leu Lys Lys Leu Glu Leu Ser Ser Asn Gln  
 175 180 185  
 10 Ile Lys Glu Phe Ser Pro Gly Cys Phe His Ala Ile Gly Arg Leu Phe  
 190 195 200  
 Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys  
 205 210 215  
 15 Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser  
 220 225 230 235  
 Asn Ser Gln Leu Ser Thr Thr Ser Asn Thr Thr Phe Leu Gly Leu Lys  
 240 245 250  
 Trp Thr Asn Leu Thr Met Leu Asp Leu Ser Tyr Asn Asn Leu Asn Val  
 255 260 265  
 25 Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe  
 270 275 280  
 Leu Glu Tyr Asn Asn Ile Gln His Leu Phe Ser His Ser Leu His Gly  
 285 290 295  
 30 Leu Phe Asn Val Arg Tyr Leu Asn Leu Lys Arg Ser Phe Thr Lys Gln  
 300 305 310 315  
 Ser Ile Ser Leu Ala Ser Leu Pro Lys Ile Asp Asp Phe Ser Phe Gln  
 320 325 330  
 Trp Leu Lys Cys Leu Glu His Leu Asn Met Glu Asp Asn Asp Ile Pro  
 335 340 345  
 40 Gly Ile Lys Ser Asn Met Phe Thr Gly Leu Ile Asn Leu Lys Tyr Leu  
 350 355 360  
 Ser Leu Ser Asn Ser Phe Thr Ser Leu Arg Thr Leu Thr Asn Glu Thr  
 365 370 375  
 45 Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys  
 380 385 390 395  
 Asn Lys Ile Ser Lys Ile Glu Ser Asp Ala Phe Ser Trp Leu Gly His  
 400 405 410  
 Leu Glu Val Leu Asp Leu Gly Leu Asn Glu Ile Gly Gln Glu Leu Thr  
 415 420 425  
 55 Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser  
 430 435 440  
 Tyr Asn Lys Tyr Leu Gln Leu Thr Arg Asn Ser Phe Ala Leu Val Pro  
 445 450 455  
 60 Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val Asp

	460		465		470		475
	Ser Ser Pro Ser	Pro Phe Gln Pro Leu Arg Asn Leu Thr Ile Leu Asp					
		480		485			490
5	Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Asp Asp Met Leu Glu Gly						
		495		500			505
10	Leu Glu Lys Leu Glu Ile Leu Asp Leu Gln His Asn Asn Leu Ala Arg						
		510		515			520
	Leu Trp Lys His Ala Asn Pro Gly Gly Pro Ile Tyr Phe Leu Lys Gly						
		525		530			535
15	Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Phe Asp Glu						
			545				555
	Ile Pro Val Glu Val Phe Lys Asp Leu Phe Glu Leu Lys Ile Ile Asp						
			560				570
20	Leu Gly Leu Asn Asn Leu Asn Thr Leu Pro Ala Ser Val Phe Asn Asn						
		575		580			585
25	Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser						
		590		595			600
	Val Glu Lys Lys Val Phe Gly Pro Ala Phe Arg Asn Leu Thr Glu Leu						
		605		610			615
30	Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ala Trp						
			625				635
	Phe Val Asn Trp Ile Asn Glu Thr His Thr Asn Ile Pro Glu Leu Ser						
			640				650
35	Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val						
		655		660			665
40	Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu						
		670		675			680
	Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val						
		685		690			695
45	Leu Leu Ile His Phe Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn Val						
			705				715
	Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu						
			720				730
50	Gln Phe Glu Tyr Ala Ala Tyr Ile Ile His Ala Tyr Lys Asp Lys Asp						
		735		740			745
55	Trp Val Trp Glu His Phe Ser Ser Met Glu Lys Glu Asp Gln Ser Leu						
		750		755			760
	Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Phe Glu Leu						
		765		770			775
60	Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val						
			785				795

	Ile	Thr	His	His	Leu 800	Leu	Lys	Asp	Pro	Leu 805	Cys	Lys	Arg	Phe	Lys 810	Val
5	His	His	Ala	Val 815	Gln	Gln	Ala	Ile	Glu 820	Gln	Asn	Leu	Asp	Ser 825	Ile	Ile
	Leu	Val	Phe 830	Leu	Glu	Glu	Ile	Pro 835	Asp	Tyr	Lys	Leu	Asn 840	His	Ala	Leu
10	Cys 845	Leu	Arg	Arg	Gly	Met	Phe 850	Lys	Ser	His	Cys	Ile 855	Leu	Asn	Trp	Pro
15	Val 860	Gln	Lys	Glu	Arg	Ile 865	Gly	Ala	Phe	Arg	His 870	Lys	Leu	Gln	Val	Ala 875
	Leu	Gly	Ser	Lys	Asn 880	Ser	Val	His								

20 (2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 2400 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS  
(B) LOCATION: 1..2397

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

40	ATG Met 1	GAG Glu	CTG Leu	AAT Asn	TTC Phe 5	TAC Tyr	AAA Lys	ATC Ile	CCC Pro	GAC Asp 10	AAC Asn	CTC Leu	CCC Pro	TTC Phe 15	TCA Ser	ACC Thr	48
45	AAG Lys	AAC Asn	CTG Leu	GAC Asp 20	CTG Leu	AGC Ser	TTT Phe	AAT Asn	CCC Pro 25	CTG Leu	AGG Arg	CAT His	TTA Leu	GGC Gly 30	AGC Ser	TAT Tyr	96
	AGC Ser	TTC Phe	TTC Phe 35	AGT Ser	TTC Phe	CCA Pro	GAA Glu	CTG Leu 40	CAG Gln	GTG Val	CTG Leu	GAT Asp 45	TTA Leu	TCC Ser	AGG Arg	TGT Cys	144
50	GAA Glu 50	ATC Ile	CAG Gln	ACA Thr	ATT Ile	GAA Glu	GAT Asp 55	GGG Gly	GCA Ala	TAT Tyr	CAG Gln	AGC Ser 60	CTA Leu	AGC Ser	CAC His	CTC Leu	192
55	TCT Ser 65	ACC Thr	TTA Leu	ATA Ile	TTG Leu	ACA Thr 70	GGA Gly	AAC Asn	CCC Pro	ATC Ile	CAG Gln 75	AGT Ser	TTA Leu	GCC Ala	CTG Leu	GGA Gly 80	240
60	GCC Ala	TTT Phe	TCT Ser	GGA Gly	CTA Leu 85	TCA Ser	AGT Ser	TTA Leu	CAG Gln 90	AAG Lys	CTG Leu	GTG Val	GCT Ala	GTG Val	GAG Glu 95	ACA Thr	288

		AAT	CTA	GCA	TCT	CTA	GAG	AAC	TTC	CCC	ATT	GGA	CAT	CTC	AAA	ACT	TTG	336
		Asn	Leu	Ala	Ser	Leu	Glu	Asn	Phe	Pro	Ile	Gly	His	Leu	Lys	Thr	Leu	
				100						105					110			
5		AAA	GAA	CTT	AAT	GTG	GCT	CAC	AAT	CTT	ATC	CAA	TCT	TTC	AAA	TTA	CCT	384
		Lys	Glu	Leu	Asn	Val	Ala	His	Asn	Leu	Ile	Gln	Ser	Phe	Lys	Leu	Pro	
				115					120					125				
10		GAG	TAT	TTT	TCT	AAT	CTG	ACC	AAT	CTA	GAG	CAC	TTG	GAC	CTT	TCC	AGC	432
		Glu	Tyr	Phe	Ser	Asn	Leu	Thr	Asn	Leu	Glu	His	Leu	Asp	Leu	Ser	Ser	
			130					135					140					
15		AAC	AAG	ATT	CAA	AGT	ATT	TAT	TGC	ACA	GAC	TTG	CGG	GTT	CTA	CAT	CAA	480
		Asn	Lys	Ile	Gln	Ser	Ile	Tyr	Cys	Thr	Asp	Leu	Arg	Val	Leu	His	Gln	
		145					150					155					160	
20		ATG	CCC	CTA	CTC	AAT	CTC	TCT	TTA	GAC	CTG	TCC	CTG	AAC	CCT	ATG	AAC	528
		Met	Pro	Leu	Leu	Asn	Leu	Ser	Leu	Asp	Leu	Ser	Leu	Asn	Pro	Met	Asn	
						165					170					175		
25		TTT	ATC	CAA	CCA	GGT	GCA	TTT	AAA	GAA	ATT	AGG	CTT	CAT	AAG	CTG	ACT	576
		Phe	Ile	Gln	Pro	Gly	Ala	Phe	Lys	Glu	Ile	Arg	Leu	His	Lys	Leu	Thr	
					180					185					190			
30		TTA	AGA	AAT	AAT	TTT	GAT	AGT	TTA	AAT	GTA	ATG	AAA	ACT	TGT	ATT	CAA	624
		Leu	Arg	Asn	Asn	Phe	Asp	Ser	Leu	Asn	Val	Met	Lys	Thr	Cys	Ile	Gln	
				195				200					205					
35		GGT	CTG	GCT	GGT	TTA	GAA	GTC	CAT	CGT	TTG	GTT	CTG	GGA	GAA	TTT	AGA	672
		Gly	Leu	Ala	Gly	Leu	Glu	Val	His	Arg	Leu	Val	Leu	Gly	Glu	Phe	Arg	
			210					215					220					
40		AAT	GAA	GGA	AAC	TTG	GAA	AAG	TTT	GAC	AAA	TCT	GCT	CTA	GAG	GGC	CTG	720
		Asn	Glu	Gly	Asn	Leu	Glu	Lys	Phe	Asp	Lys	Ser	Ala	Leu	Glu	Gly	Leu	
		225					230					235					240	
45		TGC	AAT	TTG	ACC	ATT	GAA	GAA	TTC	CGA	TTA	GCA	TAC	TTA	GAC	TAC	TAC	768
		Cys	Asn	Leu	Thr	Ile	Glu	Glu	Phe	Arg	Leu	Ala	Tyr	Leu	Asp	Tyr	Tyr	
						245					250					255		
50		CTC	GAT	GAT	ATT	ATT	GAC	TTA	TTT	AAT	TGT	TTG	ACA	AAT	GTT	TCT	TCA	816
		Leu	Asp	Asp	Ile	Ile	Asp	Leu	Phe	Asn	Cys	Leu	Thr	Asn	Val	Ser	Ser	
						260				265					270			
55		TTT	TCC	CTG	GTG	AGT	GTG	ACT	ATT	GAA	AGG	GTA	AAA	GAC	TTT	TCT	TAT	864
		Phe	Ser	Leu	Val	Ser	Val	Thr	Ile	Glu	Arg	Val	Lys	Asp	Phe	Ser	Tyr	
				275				280					285					
60		AAT	TTC	GGA	TGG	CAA	CAT	TTA	GAA	TTA	GTT	AAC	TGT	AAA	TTT	GGA	CAG	912
		Asn	Phe	Gly	Trp	Gln	His	Leu	Glu	Leu	Val	Asn	Cys	Lys	Phe	Gly	Gln	
			290					295					300					
65		TTT	CCC	ACA	TTG	AAA	CTC	AAA	TCT	CTC	AAA	AGG	CTT	ACT	TTC	ACT	TCC	960
		Phe	Pro	Thr	Leu	Lys	Leu	Lys	Ser	Leu	Lys	Arg	Leu	Thr	Phe	Thr	Ser	
		305					310					315					320	
70		AAC	AAA	GGT	GGG	AAT	GCT	TTT	TCA	GAA	GTT	GAT	CTA	CCA	AGC	CTT	GAG	1008
		Asn	Lys	Gly	Gly	Asn	Ala	Phe	Ser	Glu	Val	Asp	Leu	Pro	Ser	Leu	Glu	
						325					330					335		
75		TTT	CTA	GAT	CTC	AGT	AGA	AAT	GGC	TTG	AGT	TTC	AAA	GGT	TGC	TGT	TCT	1056

	Phe	Leu	Asp	Leu	Ser	Arg	Asn	Gly	Leu	Ser	Phe	Lys	Gly	Cys	Cys	Ser	
				340					345					350			
5	CAA	AGT	GAT	TTT	GGG	ACA	ACC	AGC	CTA	AAG	TAT	TTA	GAT	CTG	AGC	TTC	1104
	Gln	Ser	Asp	Phe	Gly	Thr	Thr	Ser	Leu	Lys	Tyr	Leu	Asp	Leu	Ser	Phe	
			355					360					365				
10	AAT	GGT	GTT	ATT	ACC	ATG	AGT	TCA	AAC	TTC	TTG	GGC	TTA	GAA	CAA	CTA	1152
	Asn	Gly	Val	Ile	Thr	Met	Ser	Ser	Asn	Phe	Leu	Gly	Leu	Glu	Gln	Leu	
			370				375					380					
15	GAA	CAT	CTG	GAT	TTC	CAG	CAT	TCC	AAT	TTG	AAA	CAA	ATG	AGT	GAG	TTT	1200
	Glu	His	Leu	Asp	Phe	Gln	His	Ser	Asn	Leu	Lys	Gln	Met	Ser	Glu	Phe	
			385			390					395					400	
	TCA	GTA	TTC	CTA	TCA	CTC	AGA	AAC	CTC	ATT	TAC	CTT	GAC	ATT	TCT	CAT	1248
	Ser	Val	Phe	Leu	Ser	Leu	Arg	Asn	Leu	Ile	Tyr	Leu	Asp	Ile	Ser	His	
					405					410					415		
20	ACT	CAC	ACC	AGA	GTT	GCT	TTC	AAT	GGC	ATC	TTC	AAT	GGC	TTG	TCC	AGT	1296
	Thr	His	Thr	Arg	Val	Ala	Phe	Asn	Gly	Ile	Phe	Asn	Gly	Leu	Ser	Ser	
				420					425					430			
25	CTC	GAA	GTC	TTG	AAA	ATG	GCT	GGC	AAT	TCT	TTC	CAG	GAA	AAC	TTC	CTT	1344
	Leu	Glu	Val	Leu	Lys	Met	Ala	Gly	Asn	Ser	Phe	Gln	Glu	Asn	Phe	Leu	
			435					440					445				
30	CCA	GAT	ATC	TTC	ACA	GAG	CTG	AGA	AAC	TTG	ACC	TTC	CTG	GAC	CTC	TCT	1392
	Pro	Asp	Ile	Phe	Thr	Glu	Leu	Arg	Asn	Leu	Thr	Phe	Leu	Asp	Leu	Ser	
		450					455					460					
35	CAG	TGT	CAA	CTG	GAG	CAG	TTG	TCT	CCA	ACA	GCA	TTT	AAC	TCA	CTC	TCC	1440
	Gln	Cys	Gln	Leu	Glu	Gln	Leu	Ser	Pro	Thr	Ala	Phe	Asn	Ser	Leu	Ser	
		465				470					475					480	
	AGT	CTT	CAG	GTA	CTA	AAT	ATG	AGC	CAC	AAC	AAC	TTC	TTT	TCA	TTG	GAT	1488
	Ser	Leu	Gln	Val	Leu	Asn	Met	Ser	His	Asn	Asn	Phe	Phe	Ser	Leu	Asp	
					485					490					495		
40	ACG	TTT	CCT	TAT	AAG	TGT	CTG	AAC	TCC	CTC	CAG	GTT	CTT	GAT	TAC	AGT	1536
	Thr	Phe	Pro	Tyr	Lys	Cys	Leu	Asn	Ser	Leu	Gln	Val	Leu	Asp	Tyr	Ser	
				500					505					510			
45	CTC	AAT	CAC	ATA	ATG	ACT	TCC	AAA	AAA	CAG	GAA	CTA	CAG	CAT	TTT	CCA	1584
	Leu	Asn	His	Ile	Met	Thr	Ser	Lys	Lys	Gln	Glu	Leu	Gln	His	Phe	Pro	
			515					520					525				
50	AGT	AGT	CTA	GCT	TTC	TTA	AAT	CTT	ACT	CAG	AAT	GAC	TTT	GCT	TGT	ACT	1632
	Ser	Ser	Leu	Ala	Phe	Leu	Asn	Leu	Thr	Gln	Asn	Asp	Phe	Ala	Cys	Thr	
			530				535					540					
55	TGT	GAA	CAC	CAG	AGT	TTC	CTG	CAA	TGG	ATC	AAG	GAC	CAG	AGG	CAG	CTC	1680
	Cys	Glu	His	Gln	Ser	Phe	Leu	Gln	Trp	Ile	Lys	Asp	Gln	Arg	Gln	Leu	
		545				550					555					560	
	TTG	GTG	GAA	GTT	GAA	CGA	ATG	GAA	TGT	GCA	ACA	CCT	TCA	GAT	AAG	CAG	1728
	Leu	Val	Glu	Val	Glu	Arg	Met	Glu	Cys	Ala	Thr	Pro	Ser	Asp	Lys	Gln	
					565					570					575		
60	GGC	ATG	CCT	GTG	CTG	AGT	TTG	AAT	ATC	ACC	TGT	CAG	ATG	AAT	AAG	ACC	1776
	Gly	Met	Pro	Val	Leu	Ser	Leu	Asn	Ile	Thr	Cys	Gln	Met	Asn	Lys	Thr	

	580							585							590							
5	ATC	ATT	GGT	GTG	TCG	GTC	CTC	AGT	GTG	CTT	GTA	GTA	TCT	GTT	GTA	GCA						1824
	Ile	Ile	Gly	Val	Ser	Val	Leu	Ser	Val	Leu	Val	Val	Ser	Val	Val	Ala						
			595					600					605									
10	GTT	CTG	GTC	TAT	AAG	TTC	TAT	TTT	CAC	CTG	ATG	CTT	CTT	GCT	GGC	TGC						1872
	Val	Leu	Val	Tyr	Lys	Phe	Tyr	Phe	His	Leu	Met	Leu	Leu	Ala	Gly	Cys						
		610					615					620										
15	ATA	AAG	TAT	GGT	AGA	GGT	GAA	AAC	ATC	TAT	GAT	GCC	TTT	GTT	ATC	TAC						1920
	Ile	Lys	Tyr	Gly	Arg	Gly	Glu	Asn	Ile	Tyr	Asp	Ala	Phe	Val	Ile	Tyr						
	625					630					635					640						
20	TCA	AGC	CAG	GAT	GAG	GAC	TGG	GTA	AGG	AAT	GAG	CTA	GTA	AAG	AAT	TTA						1968
	Ser	Ser	Gln	Asp	Glu	Asp	Trp	Val	Arg	Asn	Glu	Leu	Val	Lys	Asn	Leu						
					645					650					655							
25	GAA	GAA	GGG	GTG	CCT	CCA	TTT	CAG	CTC	TGC	CTT	CAC	TAC	AGA	GAC	TTT						2016
	Glu	Glu	Gly	Val	Pro	Pro	Phe	Gln	Leu	Cys	Leu	His	Tyr	Arg	Asp	Phe						
				660					665					670								
30	ATT	CCC	GGT	GTG	GCC	ATT	GCT	GCC	AAC	ATC	ATC	CAT	GAA	GGT	TTC	CAT						2064
	Ile	Pro	Gly	Val	Ala	Ile	Ala	Ala	Asn	Ile	Ile	His	Glu	Gly	Phe	His						
			675					680					685									
35	AAA	AGC	CGA	AAG	GTG	ATT	GTT	GTG	GTG	TCC	CAG	CAC	TTC	ATC	CAG	AGC						2112
	Lys	Ser	Arg	Lys	Val	Ile	Val	Val	Val	Ser	Gln	His	Phe	Ile	Gln	Ser						
		690					695					700										
40	CGC	TGG	TGT	ATC	TTT	GAA	TAT	GAG	ATT	GCT	CAG	ACC	TGG	CAG	TTT	CTG						2160
	Arg	Trp	Cys	Ile	Phe	Glu	Tyr	Glu	Ile	Ala	Gln	Thr	Trp	Gln	Phe	Leu						
	705				710					715					720							
45	AGC	AGT	CGT	GCT	GGT	ATC	ATC	TTC	ATT	GTC	CTG	CAG	AAG	GTG	GAG	AAG						2208
	Ser	Ser	Arg	Ala	Gly	Ile	Ile	Phe	Ile	Val	Leu	Gln	Lys	Val	Glu	Lys						
				725						730					735							
50	ACC	CTG	CTC	AGG	CAG	CAG	GTG	GAG	CTG	TAC	CGC	CTT	CTC	AGC	AGG	AAC						2256
	Thr	Leu	Leu	Arg	Gln	Gln	Val	Glu	Leu	Tyr	Arg	Leu	Leu	Ser	Arg	Asn						
				740					745					750								
55	ACT	TAC	CTG	GAG	TGG	GAG	GAC	AGT	GTC	CTG	GGG	CGG	CAC	ATC	TTC	TGG						2304
	Thr	Tyr	Leu	Glu	Trp	Glu	Asp	Ser	Val	Leu	Gly	Arg	His	Ile	Phe	Trp						
			755					760					765									
60	AGA	CGA	CTC	AGA	AAA	GCC	CTG	CTG	GAT	GGT	AAA	TCA	TGG	AAT	CCA	GAA						2352
	Arg	Arg	Leu	Arg	Lys	Ala	Leu	Leu	Asp	Gly	Lys	Ser	Trp	Asn	Pro	Glu						
		770					775					780										
65	GGA	ACA	GTG	GGT	ACA	GGA	TGC	AAT	TGG	CAG	GAA	GCA	ACA	TCT	ATC							2397
	Gly	Thr	Val	Gly	Thr	Gly	Cys	Asn	Trp	Gln	Glu	Ala	Thr	Ser	Ile							
	785					790					795											
70	TGA																					2400

(2) INFORMATION FOR SEQ ID NO:8:

60

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 799 amino acids



(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

10	Met	Glu	Leu	Asn	Phe	Tyr	Lys	Ile	Pro	Asp	Asn	Leu	Pro	Phe	Ser	Thr	1	5	10	15
	Lys	Asn	Leu	Asp	Leu	Ser	Phe	Asn	Pro	Leu	Arg	His	Leu	Gly	Ser	Tyr	20	25	30	
15	Ser	Phe	Phe	Ser	Phe	Pro	Glu	Leu	Gln	Val	Leu	Asp	Leu	Ser	Arg	Cys	35	40	45	
	Glu	Ile	Gln	Thr	Ile	Glu	Asp	Gly	Ala	Tyr	Gln	Ser	Leu	Ser	His	Leu	50	55	60	
20	Ser	Thr	Leu	Ile	Leu	Thr	Gly	Asn	Pro	Ile	Gln	Ser	Leu	Ala	Leu	Gly	65	70	75	80
	Ala	Phe	Ser	Gly	Leu	Ser	Ser	Leu	Gln	Lys	Leu	Val	Ala	Val	Glu	Thr	85	90	95	
25	Asn	Leu	Ala	Ser	Leu	Glu	Asn	Phe	Pro	Ile	Gly	His	Leu	Lys	Thr	Leu	100	105	110	
	Lys	Glu	Leu	Asn	Val	Ala	His	Asn	Leu	Ile	Gln	Ser	Phe	Lys	Leu	Pro	115	120	125	
30	Glu	Tyr	Phe	Ser	Asn	Leu	Thr	Asn	Leu	Glu	His	Leu	Asp	Leu	Ser	Ser	130	135	140	
	Asn	Lys	Ile	Gln	Ser	Ile	Tyr	Cys	Thr	Asp	Leu	Arg	Val	Leu	His	Gln	145	150	155	160
35	Met	Pro	Leu	Leu	Asn	Leu	Ser	Leu	Asp	Leu	Ser	Leu	Asn	Pro	Met	Asn	165	170	175	
40	Phe	Ile	Gln	Pro	Gly	Ala	Phe	Lys	Glu	Ile	Arg	Leu	His	Lys	Leu	Thr	180	185	190	
	Leu	Arg	Asn	Asn	Phe	Asp	Ser	Leu	Asn	Val	Met	Lys	Thr	Cys	Ile	Gln	195	200	205	
45	Gly	Leu	Ala	Gly	Leu	Glu	Val	His	Arg	Leu	Val	Leu	Gly	Glu	Phe	Arg	210	215	220	
	Asn	Glu	Gly	Asn	Leu	Glu	Lys	Phe	Asp	Lys	Ser	Ala	Leu	Glu	Gly	Leu	225	230	235	240
50	Cys	Asn	Leu	Thr	Ile	Glu	Glu	Phe	Arg	Leu	Ala	Tyr	Leu	Asp	Tyr	Tyr	245	250	255	
55	Leu	Asp	Asp	Ile	Ile	Asp	Leu	Phe	Asn	Cys	Leu	Thr	Asn	Val	Ser	Ser	260	265	270	
	Phe	Ser	Leu	Val	Ser	Val	Thr	Ile	Glu	Arg	Val	Lys	Asp	Phe	Ser	Tyr	275	280	285	

60

	Asn	Phe	Gly	Trp	Gln	His	Leu	Glu	Leu	Val	Asn	Cys	Lys	Phe	Gly	Gln
	290						295				300					
5	Phe	Pro	Thr	Leu	Lys	Leu	Lys	Ser	Leu	Lys	Arg	Leu	Thr	Phe	Thr	Ser
	305					310					315					320
	Asn	Lys	Gly	Gly	Asn	Ala	Phe	Ser	Glu	Val	Asp	Leu	Pro	Ser	Leu	Glu
					325					330					335	
10	Phe	Leu	Asp	Leu	Ser	Arg	Asn	Gly	Leu	Ser	Phe	Lys	Gly	Cys	Cys	Ser
				340					345					350		
	Gln	Ser	Asp	Phe	Gly	Thr	Thr	Ser	Leu	Lys	Tyr	Leu	Asp	Leu	Ser	Phe
15			355					360					365			
	Asn	Gly	Val	Ile	Thr	Met	Ser	Ser	Asn	Phe	Leu	Gly	Leu	Glu	Gln	Leu
	370						375					380				
20	Glu	His	Leu	Asp	Phe	Gln	His	Ser	Asn	Leu	Lys	Gln	Met	Ser	Glu	Phe
	385					390					395					400
	Ser	Val	Phe	Leu	Ser	Leu	Arg	Asn	Leu	Ile	Tyr	Leu	Asp	Ile	Ser	His
					405					410				415		
25	Thr	His	Thr	Arg	Val	Ala	Phe	Asn	Gly	Ile	Phe	Asn	Gly	Leu	Ser	Ser
				420					425					430		
	Leu	Glu	Val	Leu	Lys	Met	Ala	Gly	Asn	Ser	Phe	Gln	Glu	Asn	Phe	Leu
30			435					440					445			
	Pro	Asp	Ile	Phe	Thr	Glu	Leu	Arg	Asn	Leu	Thr	Phe	Leu	Asp	Leu	Ser
	450						455					460				
35	Gln	Cys	Gln	Leu	Glu	Gln	Leu	Ser	Pro	Thr	Ala	Phe	Asn	Ser	Leu	Ser
	465					470					475					480
	Ser	Leu	Gln	Val	Leu	Asn	Met	Ser	His	Asn	Asn	Phe	Phe	Ser	Leu	Asp
					485					490					495	
40	Thr	Phe	Pro	Tyr	Lys	Cys	Leu	Asn	Ser	Leu	Gln	Val	Leu	Asp	Tyr	Ser
				500					505					510		
	Leu	Asn	His	Ile	Met	Thr	Ser	Lys	Lys	Gln	Glu	Leu	Gln	His	Phe	Pro
45			515					520					525			
	Ser	Ser	Leu	Ala	Phe	Leu	Asn	Leu	Thr	Gln	Asn	Asp	Phe	Ala	Cys	Thr
	530						535					540				
50	Cys	Glu	His	Gln	Ser	Phe	Leu	Gln	Trp	Ile	Lys	Asp	Gln	Arg	Gln	Leu
	545					550					555					560
	Leu	Val	Glu	Val	Glu	Arg	Met	Glu	Cys	Ala	Thr	Pro	Ser	Asp	Lys	Gln
					565				570						575	
55	Gly	Met	Pro	Val	Leu	Ser	Leu	Asn	Ile	Thr	Cys	Gln	Met	Asn	Lys	Thr
				580					585					590		
	Ile	Ile	Gly	Val	Ser	Val	Leu	Ser	Val	Leu	Val	Val	Ser	Val	Val	Ala
60			595					600					605			
	Val	Leu	Val	Tyr	Lys	Phe	Tyr	Phe	His	Leu	Met	Leu	Leu	Ala	Gly	Cys

	610	615	620	
5	Ile Lys Tyr Gly Arg	Gly Glu Asn Ile Tyr	Asp Ala Phe Val Ile Tyr	625 630 635 640
	Ser Ser Gln Asp	Glu Asp Trp Val Arg	Asn Glu Leu Val Lys Asn Leu	645 650 655
10	Glu Glu Gly Val	Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe		660 665 670
	Ile Pro Gly Val	Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His		675 680 685
15	Lys Ser Arg Lys Val	Ile Val Val Val Ser Gln His Phe Ile Gln Ser		690 695 700
	Arg Trp Cys Ile Phe	Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu		705 710 715 720
20	Ser Ser Arg Ala Gly	Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys		725 730 735
	Thr Leu Leu Arg	Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn		740 745 750
25	Thr Tyr Leu Glu Trp	Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp		755 760 765
30	Arg Arg Leu Arg Lys	Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu		770 775 780
	Gly Thr Val Gly Thr	Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile		785 790 795

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- 40 (A) LENGTH: 1275 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

45

## (ix) FEATURE:

- 50 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..1095

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

55	TGT TGG GAT GTT TTT GAG GGA CTT TCT CAT CTT CAA GTT CTG TAT TTG	48
	Cys Trp Asp Val Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu	
	1 5 10 15	
60	AAT CAT AAC TAT CTT AAT TCC CTT CCA CCA GGA GTA TTT AGC CAT CTG	96
	Asn His Asn Tyr Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu	
	20 25 30	

	ACT	GCA	TTA	AGG	GGA	CTA	AGC	CTC	AAC	TCC	AAC	AGG	CTG	ACA	GTT	CTT	144
	Thr	Ala	Leu	Arg	Gly	Leu	Ser	Leu	Asn	Ser	Asn	Arg	Leu	Thr	Val	Leu	
			35					40					45				
5	TCT	CAC	AAT	GAT	TTA	CCT	GCT	AAT	TTA	GAG	ATC	CTG	GAC	ATA	TCC	AGG	192
	Ser	His	Asn	Asp	Leu	Pro	Ala	Asn	Leu	Glu	Ile	Leu	Asp	Ile	Ser	Arg	
		50					55					60					
10	AAC	CAG	CTC	CTA	GCT	CCT	AAT	CCT	GAT	GTA	TTT	GTA	TCA	CTT	AGT	GTC	240
	Asn	Gln	Leu	Leu	Ala	Pro	Asn	Pro	Asp	Val	Phe	Val	Ser	Leu	Ser	Val	
	65					70				75						80	
15	TTG	GAT	ATA	ACT	CAT	AAC	AAG	TTC	ATT	TGT	GAA	TGT	GAA	CTT	AGC	ACT	288
	Leu	Asp	Ile	Thr	His	Asn	Lys	Phe	Ile	Cys	Glu	Cys	Glu	Leu	Ser	Thr	
					85					90					95		
20	TTT	ATC	AAT	TGG	CTT	AAT	CAC	ACC	AAT	GTC	ACT	ATA	GCT	GGG	CCT	CCT	336
	Phe	Ile	Asn	Trp	Leu	Asn	His	Thr	Asn	Val	Thr	Ile	Ala	Gly	Pro	Pro	
				100					105					110			
	GCA	GAC	ATA	TAT	TGT	GTG	TAC	CCT	GAC	TCG	TTC	TCT	GGG	GTT	TCC	CTC	384
	Ala	Asp	Ile	Tyr	Cys	Val	Tyr	Pro	Asp	Ser	Phe	Ser	Gly	Val	Ser	Leu	
			115					120					125				
25	TTC	TCT	CTT	TCC	ACG	GAA	GGT	TGT	GAT	GAA	GAG	GAA	GTC	TTA	AAG	TCC	432
	Phe	Ser	Leu	Ser	Thr	Glu	Gly	Cys	Asp	Glu	Glu	Glu	Val	Leu	Lys	Ser	
		130					135					140					
30	CTA	AAG	TTC	TCC	CTT	TTC	ATT	GTA	TGC	ACT	GTC	ACT	CTG	ACT	CTG	TTC	480
	Leu	Lys	Phe	Ser	Leu	Phe	Ile	Val	Cys	Thr	Val	Thr	Leu	Thr	Leu	Phe	
	145					150					155					160	
35	CTC	ATG	ACC	ATC	CTC	ACA	GTC	ACA	AAG	TTC	CGG	GGC	TTC	TGT	TTT	ATC	528
	Leu	Met	Thr	Ile	Leu	Thr	Val	Thr	Lys	Phe	Arg	Gly	Phe	Cys	Phe	Ile	
					165					170					175		
40	TGT	TAT	AAG	ACA	GCC	CAG	AGA	CTG	GTG	TTC	AAG	GAC	CAT	CCC	CAG	GGC	576
	Cys	Tyr	Lys	Thr	Ala	Gln	Arg	Leu	Val	Phe	Lys	Asp	His	Pro	Gln	Gly	
				180					185					190			
	ACA	GAA	CCT	GAT	ATG	TAC	AAA	TAT	GAT	GCC	TAT	TTG	TGC	TTC	AGC	AGC	624
	Thr	Glu	Pro	Asp	Met	Tyr	Lys	Tyr	Asp	Ala	Tyr	Leu	Cys	Phe	Ser	Ser	
			195					200					205				
45	AAA	GAC	TTC	ACA	TGG	GTG	CAG	AAT	GCT	TTG	CTC	AAA	CAC	CTG	GAC	ACT	672
	Lys	Asp	Phe	Thr	Trp	Val	Gln	Asn	Ala	Leu	Leu	Lys	His	Leu	Asp	Thr	
		210					215					220					
50	CAA	TAC	AGT	GAC	CAA	AAC	AGA	TTC	AAC	CTG	TGC	TTT	GAA	GAA	AGA	GAC	720
	Gln	Tyr	Ser	Asp	Gln	Asn	Arg	Phe	Asn	Leu	Cys	Phe	Glu	Glu	Arg	Asp	
	225					230					235					240	
55	TTT	GTC	CCA	GGA	GAA	AAC	CGC	ATT	GCC	AAT	ATC	CAG	GAT	GCC	ATC	TGG	768
	Phe	Val	Pro	Gly	Glu	Asn	Arg	Ile	Ala	Asn	Ile	Gln	Asp	Ala	Ile	Trp	
				245						250					255		
60	AAC	AGT	AGA	AAG	ATC	GTT	TGT	CTT	GTG	AGC	AGA	CAC	TTC	CTT	AGA	GAT	816
	Asn	Ser	Arg	Lys	Ile	Val	Cys	Leu	Val	Ser	Arg	His	Phe	Leu	Arg	Asp	
				260					265					270			
	GGC	TGG	TGC	CTT	GAA	GCC	TTC	AGT	TAT	GCC	CAG	GGC	AGG	TGC	TTA	TCT	864

	Gly Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser	
	275 280 285	
5	GAC CTT AAC AGT GCT CTC ATC ATG GTG GTG GTT GGG TCC TTG TCC CAG Asp Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln	912
	290 295 300	
10	TAC CAG TTG ATG AAA CAT CAA TCC ATC AGA GGC TTT GTA CAG AAA CAG Tyr Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln	960
	305 310 315 320	
15	CAG TAT TTG AGG TGG CCT GAG GAT CTC CAG GAT GTT GGC TGG TTT CTT Gln Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu	1008
	325 330 335	
	CAT AAA CTC TCT CAA CAG ATA CTA AAG AAA GAA AAG GAA AAG AAG AAA His Lys Leu Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys	1056
	340 345 350	
20	GAC AAT AAC ATT CCG TTG CAA ACT GTA GCA ACC ATC TCC TAATCAAAGG Asp Asn Asn Ile Pro Leu Gln Thr Val Ala Thr Ile Ser	1105
	355 360 365	
25	AGCAATTTCC AACTTATCTC AAGCCACAAA TAACTCTTCA CTTTGTATTT GCACCAAGTT	1165
	ATCATTTTGG GGTCTCTCTT GGAGGTTTTT TTTTCTTTT TGCTACTATG AAAACAACAT	1225
	AAATCTCTCA ATTTTCGTAT CAAAAAAAAA AAAAAAAAAA TGGCGGCCGC	1275
30	(2) INFORMATION FOR SEQ ID NO:10:	
	(i) SEQUENCE CHARACTERISTICS:	
35	(A) LENGTH: 365 amino acids	
	(B) TYPE: amino acid	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: protein	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:	
	Cys Trp Asp Val Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu	
	1 5 10 15	
45	Asn His Asn Tyr Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu	
	20 25 30	
	Thr Ala Leu Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu	
50	35 40 45	
	Ser His Asn Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg	
	50 55 60	
55	Asn Gln Leu Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val	
	65 70 75 80	
	Leu Asp Ile Thr His Asn Lys Phe Ile Cys Glu Cys Glu Leu Ser Thr	
	85 90 95	
60	Phe Ile Asn Trp Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro	
	100 105 110	

Ala Asp Ile Tyr Cys Val Tyr Pro Asp Ser Phe Ser Gly Val Ser Leu  
 115 120 125

5 Phe Ser Leu Ser Thr Glu Gly Cys Asp Glu Glu Glu Val Leu Lys Ser  
 130 135 140

Leu Lys Phe Ser Leu Phe Ile Val Cys Thr Val Thr Leu Thr Leu Phe  
 145 150 155 160

10 Leu Met Thr Ile Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile  
 165 170 175

Cys Tyr Lys Thr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly  
 180 185 190

15 Thr Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser  
 195 200 205

20 Lys Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr  
 210 215 220

Gln Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp  
 225 230 235 240

25 Phe Val Pro Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp  
 245 250 255

Asn Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp  
 260 265 270

30 Gly Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser  
 275 280 285

35 Asp Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln  
 290 295 300

Tyr Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln  
 305 310 315 320

40 Gln Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu  
 325 330 335

His Lys Leu Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys  
 340 345 350

45 Asp Asn Asn Ile Pro Leu Gln Thr Val Ala Thr Ile Ser  
 355 360 365

50 (2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 3138 base pairs  
 (B) TYPE: nucleic acid  
 55 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

60

(ix) FEATURE:

(A) NAME/KEY: CDS  
(B) LOCATION: 1..3135

## (ix) FEATURE:

5 (A) NAME/KEY: mat\_peptide  
(B) LOCATION: 67..3135

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

10	ATG TGG ACA CTG AAG AGA CTA ATT CTT ATC CTT TTT AAC ATA ATC CTA	48
	Met Trp Thr Leu Lys Arg Leu Ile Leu Ile Leu Phe Asn Ile Ile Leu	
	-22 -20 -15 -10	
15	ATT TCC AAA CTC CTT GGG GCT AGA TGG TTT CCT AAA ACT CTG CCC TGT	96
	Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys Thr Leu Pro Cys	
	-5 1 5 10	
20	GAT GTC ACT CTG GAT GTT CCA AAG AAC CAT GTG ATC GTG GAC TGC ACA	144
	Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile Val Asp Cys Thr	
	15 20 25	
25	GAC AAG CAT TTG ACA GAA ATT CCT GGA GGT ATT CCC ACG AAC ACC ACG	192
	Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro Thr Asn Thr Thr	
	30 35 40	
30	AAC CTC ACC CTC ACC ATT AAC CAC ATA CCA GAC ATC TCC CCA GCG TCC	240
	Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile Ser Pro Ala Ser	
	45 50 55	
35	TTT CAC AGA CTG GAC CAT CTG GTA GAG ATC GAT TTC AGA TGC AAC TGT	288
	Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe Arg Cys Asn Cys	
	60 65 70	
40	GTA CCT ATT CCA CTG GGG TCA AAA AAC AAC ATG TGC ATC AAG AGG CTG	336
	Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys Ile Lys Arg Leu	
	75 80 85 90	
45	CAG ATT AAA CCC AGA AGC TTT AGT GGA CTC ACT TAT TTA AAA TCC CTT	384
	Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr Leu Lys Ser Leu	
	95 100 105	
50	TAC CTG GAT GGA AAC CAG CTA CTA GAG ATA CCG CAG GGC CTC CCG CCT	432
	Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln Gly Leu Pro Pro	
	110 115 120	
55	AGC TTA CAG CTT CTC AGC CTT GAG GCC AAC AAC ATC TTT TCC ATC AGA	480
	Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile Phe Ser Ile Arg	
	125 130 135	
60	AAA GAG AAT CTA ACA GAA CTG GCC AAC ATA GAA ATA CTC TAC CTG GGC	528
	Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile Leu Tyr Leu Gly	
	140 145 150	
65	CAA AAC TGT TAT TAT CGA AAT CCT TGT TAT GTT TCA TAT TCA ATA GAG	576
	Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser Tyr Ser Ile Glu	
	155 160 165 170	
70	AAA GAT GCC TTC CTA AAC TTG ACA AAG TTA AAA GTG CTC TCC CTG AAA	624
	Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val Leu Ser Leu Lys	
	175 180 185	

5	GAT	AAC	AAT	GTC	ACA	GCC	GTC	CCT	ACT	GTT	TTG	CCA	TCT	ACT	TTA	ACA	672
	Asp	Asn	Asn	Val	Thr	Ala	Val	Pro	Thr	Val	Leu	Pro	Ser	Thr	Leu	Thr	
				190					195					200			
10	GAA	CTA	TAT	CTC	TAC	AAC	AAC	ATG	ATT	GCA	AAA	ATC	CAA	GAA	GAT	GAT	720
	Glu	Leu	Tyr	Leu	Tyr	Asn	Asn	Met	Ile	Ala	Lys	Ile	Gln	Glu	Asp	Asp	
			205					210					215				
15	TTT	AAT	AAC	CTC	AAC	CAA	TTA	CAA	ATT	CTT	GAC	CTA	AGT	GGA	AAT	TGC	768
	Phe	Asn	Asn	Leu	Asn	Gln	Leu	Gln	Ile	Leu	Asp	Leu	Ser	Gly	Asn	Cys	
			220				225					230					
20	CCT	CGT	TGT	TAT	AAT	GCC	CCA	TTT	CCT	TGT	GCG	CCG	TGT	AAA	AAT	AAT	816
	Pro	Arg	Cys	Tyr	Asn	Ala	Pro	Phe	Pro	Cys	Ala	Pro	Cys	Lys	Asn	Asn	
						240					245					250	
25	TCT	CCC	CTA	CAG	ATC	CCT	GTA	AAT	GCT	TTT	GAT	GCG	CTG	ACA	GAA	TTA	864
	Ser	Pro	Leu	Gln	Ile	Pro	Val	Asn	Ala	Phe	Asp	Ala	Leu	Thr	Glu	Leu	
					255					260					265		
30	AAA	GTT	TTA	CGT	CTA	CAC	AGT	AAC	TCT	CTT	CAG	CAT	GTG	CCC	CCA	AGA	912
	Lys	Val	Leu	Arg	Leu	His	Ser	Asn	Ser	Leu	Gln	His	Val	Pro	Pro	Arg	
				270					275					280			
35	TGG	TTT	AAG	AAC	ATC	AAC	AAA	CTC	CAG	GAA	CTG	GAT	CTG	TCC	CAA	AAC	960
	Trp	Phe	Lys	Asn	Ile	Asn	Lys	Leu	Gln	Glu	Leu	Asp	Leu	Ser	Gln	Asn	
			285					290					295				
40	TTC	TTG	GCC	AAA	GAA	ATT	GGG	GAT	GCT	AAA	TTT	CTG	CAT	TTT	CTC	CCC	1008
	Phe	Leu	Ala	Lys	Glu	Ile	Gly	Asp	Ala	Lys	Phe	Leu	His	Phe	Leu	Pro	
			300				305					310					
45	AGC	CTC	ATC	CAA	TTG	GAT	CTG	TCT	TTC	AAT	TTT	GAA	CTT	CAG	GTC	TAT	1056
	Ser	Leu	Ile	Gln	Leu	Asp	Leu	Ser	Phe	Asn	Phe	Glu	Leu	Gln	Val	Tyr	
						320					325					330	
50	CGT	GCA	TCT	ATG	AAT	CTA	TCA	CAA	GCA	TTT	TCT	TCA	CTG	AAA	AGC	CTG	1104
	Arg	Ala	Ser	Met	Asn	Leu	Ser	Gln	Ala	Phe	Ser	Ser	Leu	Lys	Ser	Leu	
					335					340					345		
55	AAA	ATT	CTG	CGG	ATC	AGA	GGA	TAT	GTC	TTT	AAA	GAG	TTG	AAA	AGC	TTT	1152
	Lys	Ile	Leu	Arg	Ile	Arg	Gly	Tyr	Val	Phe	Lys	Glu	Leu	Lys	Ser	Phe	
				350					355					360			
60	AAC	CTC	TCG	CCA	TTA	CAT	AAT	CTT	CAA	AAT	CTT	GAA	GTT	CTT	GAT	CTT	1200
	Asn	Leu	Ser	Pro	Leu	His	Asn	Leu	Gln	Asn	Leu	Glu	Val	Leu	Asp	Leu	
				365				370					375				
65	GGC	ACT	AAC	TTT	ATA	AAA	ATT	GCT	AAC	CTC	AGC	ATG	TTT	AAA	CAA	TTT	1248
	Gly	Thr	Asn	Phe	Ile	Lys	Ile	Ala	Asn	Leu	Ser	Met	Phe	Lys	Gln	Phe	
				380			385					390					
70	AAA	AGA	CTG	AAA	GTC	ATA	GAT	CTT	TCA	GTG	AAT	AAA	ATA	TCA	CCT	TCA	1296
	Lys	Arg	Leu	Lys	Val	Ile	Asp	Leu	Ser	Val	Asn	Lys	Ile	Ser	Pro	Ser	
						400					405					410	
75	GGA	GAT	TCA	AGT	GAA	GTT	GGC	TTC	TGC	TCA	AAT	GCC	AGA	ACT	TCT	GTA	1344
	Gly	Asp	Ser	Ser	Glu	Val	Gly	Phe	Cys	Ser	Asn	Ala	Arg	Thr	Ser	Val	
					415					420					425		



		GAA	AGT	TAT	GAA	CCC	CAG	GTC	CTG	GAA	CAA	TTA	CAT	TAT	TTC	AGA	TAT	1392
		Glu	Ser	Tyr	Glu	Pro	Gln	Val	Leu	Glu	Gln	Leu	His	Tyr	Phe	Arg	Tyr	
					430					435					440			
5		GAT	AAG	TAT	GCA	AGG	AGT	TGC	AGA	TTC	AAA	AAC	AAA	GAG	GCT	TCT	TTC	1440
		Asp	Lys	Tyr	Ala	Arg	Ser	Cys	Arg	Phe	Lys	Asn	Lys	Glu	Ala	Ser	Phe	
				445					450					455				
10		ATG	TCT	GTT	AAT	GAA	AGC	TGC	TAC	AAG	TAT	GGG	CAG	ACC	TTG	GAT	CTA	1488
		Met	Ser	Val	Asn	Glu	Ser	Cys	Tyr	Lys	Tyr	Gly	Gln	Thr	Leu	Asp	Leu	
			460					465					470					
15		AGT	AAA	AAT	AGT	ATA	TTT	TTT	GTC	AAG	TCC	TCT	GAT	TTT	CAG	CAT	CTT	1536
		Ser	Lys	Asn	Ser	Ile	Phe	Phe	Val	Lys	Ser	Ser	Asp	Phe	Gln	His	Leu	
		475				480						485					490	
20		TCT	TTC	CTC	AAA	TGC	CTG	AAT	CTG	TCA	GGA	AAT	CTC	ATT	AGC	CAA	ACT	1584
		Ser	Phe	Leu	Lys	Cys	Leu	Asn	Leu	Ser	Gly	Asn	Leu	Ile	Ser	Gln	Thr	
					495						500					505		
		CTT	AAT	GGC	AGT	GAA	TTC	CAA	CCT	TTA	GCA	GAG	CTG	AGA	TAT	TTG	GAC	1632
		Leu	Asn	Gly	Ser	Glu	Phe	Gln	Pro	Leu	Ala	Glu	Leu	Arg	Tyr	Leu	Asp	
					510				515					520				
25		TTC	TCC	AAC	AAC	CGG	CTT	GAT	TTA	CTC	CAT	TCA	ACA	GCA	TTT	GAA	GAG	1680
		Phe	Ser	Asn	Asn	Arg	Leu	Asp	Leu	Leu	His	Ser	Thr	Ala	Phe	Glu	Glu	
				525					530					535				
30		CTT	CAC	AAA	CTG	GAA	GTT	CTG	GAT	ATA	AGC	AGT	AAT	AGC	CAT	TAT	TTT	1728
		Leu	His	Lys	Leu	Glu	Val	Leu	Asp	Ile	Ser	Ser	Asn	Ser	His	Tyr	Phe	
			540					545					550					
35		CAA	TCA	GAA	GGA	ATT	ACT	CAT	ATG	CTA	AAC	TTT	ACC	AAG	AAC	CTA	AAG	1776
		Gln	Ser	Glu	Gly	Ile	Thr	His	Met	Leu	Asn	Phe	Thr	Lys	Asn	Leu	Lys	
		555				560						565					570	
40		GTT	CTG	CAG	AAA	CTG	ATG	ATG	AAC	GAC	AAT	GAC	ATC	TCT	TCC	TCC	ACC	1824
		Val	Leu	Gln	Lys	Leu	Met	Met	Asn	Asp	Asn	Asp	Ile	Ser	Ser	Ser	Thr	
					575						580						585	
		AGC	AGG	ACC	ATG	GAG	AGT	GAG	TCT	CTT	AGA	ACT	CTG	GAA	TTC	AGA	GGA	1872
		Ser	Arg	Thr	Met	Glu	Ser	Glu	Ser	Leu	Arg	Thr	Leu	Glu	Phe	Arg	Gly	
					590					595					600			
45		AAT	CAC	TTA	GAT	GTT	TTA	TGG	AGA	GAA	GGT	GAT	AAC	AGA	TAC	TTA	CAA	1920
		Asn	His	Leu	Asp	Val	Leu	Trp	Arg	Glu	Gly	Asp	Asn	Arg	Tyr	Leu	Gln	
				605				610						615				
50		TTA	TTC	AAG	AAT	CTG	CTA	AAA	TTA	GAG	GAA	TTA	GAC	ATC	TCT	AAA	AAT	1968
		Leu	Phe	Lys	Asn	Leu	Leu	Lys	Leu	Glu	Glu	Leu	Asp	Ile	Ser	Lys	Asn	
			620					625					630					
55		TCC	CTA	AGT	TTC	TTG	CCT	TCT	GGA	GTT	TTT	GAT	GGT	ATG	CCT	CCA	AAT	2016
		Ser	Leu	Ser	Phe	Leu	Pro	Ser	Gly	Val	Phe	Asp	Gly	Met	Pro	Pro	Asn	
		635					640					645					650	
60		CTA	AAG	AAT	CTC	TCT	TTG	GCC	AAA	AAT	GGG	CTC	AAA	TCT	TTC	AGT	TGG	2064
		Leu	Lys	Asn	Leu	Ser	Leu	Ala	Lys	Asn	Gly	Leu	Lys	Ser	Phe	Ser	Trp	
					655						660					665		
		AAG	AAA	CTC	CAG	TGT	CTA	AAG	AAC	CTG	GAA	ACT	TTG	GAC	CTC	AGC	CAC	2112

		Lys	Lys	Leu	Gln	Cys	Leu	Lys	Asn	Leu	Glu	Thr	Leu	Asp	Leu	Ser	His	
					670					675					680			
5		AAC	CAA	CTG	ACC	ACT	GTC	CCT	GAG	AGA	TTA	TCC	AAC	TGT	TCC	AGA	AGC	2160
		Asn	Gln	Leu	Thr	Thr	Val	Pro	Glu	Arg	Leu	Ser	Asn	Cys	Ser	Arg	Ser	
				685					690					695				
10		CTC	AAG	AAT	CTG	ATT	CTT	AAG	AAT	AAT	CAA	ATC	AGG	AGT	CTG	ACG	AAG	2208
		Leu	Lys	Asn	Leu	Ile	Leu	Lys	Asn	Asn	Gln	Ile	Arg	Ser	Leu	Thr	Lys	
			700					705					710					
15		TAT	TTT	CTA	CAA	GAT	GCC	TTC	CAG	TTG	CGA	TAT	CTG	GAT	CTC	AGC	TCA	2256
		Tyr	Phe	Leu	Gln	Asp	Ala	Phe	Gln	Leu	Arg	Tyr	Leu	Asp	Leu	Ser	Ser	
		715				720					725						730	
		AAT	AAA	ATC	CAG	ATG	ATC	CAA	AAG	ACC	AGC	TTC	CCA	GAA	AAT	GTC	CTC	2304
		Asn	Lys	Ile	Gln	Met	Ile	Gln	Lys	Thr	Ser	Phe	Pro	Glu	Asn	Val	Leu	
						735					740					745		
20		AAC	AAT	CTG	AAG	ATG	TTG	CTT	TTG	CAT	CAT	AAT	CGG	TTT	CTG	TGC	ACC	2352
		Asn	Asn	Leu	Lys	Met	Leu	Leu	Leu	His	His	Asn	Arg	Phe	Leu	Cys	Thr	
					750					755					760			
25		TGT	GAT	GCT	GTG	TGG	TTT	GTC	TGG	TGG	GTT	AAC	CAT	ACG	GAG	GTG	ACT	2400
		Cys	Asp	Ala	Val	Trp	Phe	Val	Trp	Trp	Val	Asn	His	Thr	Glu	Val	Thr	
				765					770					775				
30		ATT	CCT	TAC	CTG	GCC	ACA	GAT	GTG	ACT	TGT	GTG	GGG	CCA	GGA	GCA	CAC	2448
		Ile	Pro	Tyr	Leu	Ala	Thr	Asp	Val	Thr	Cys	Val	Gly	Pro	Gly	Ala	His	
			780					785					790					
35		AAG	GGC	CAA	AGT	GTG	ATC	TCC	CTG	GAT	CTG	TAC	ACC	TGT	GAG	TTA	GAT	2496
		Lys	Gly	Gln	Ser	Val	Ile	Ser	Leu	Asp	Leu	Tyr	Thr	Cys	Glu	Leu	Asp	
		795				800					805						810	
		CTG	ACT	AAC	CTG	ATT	CTG	TTC	TCA	CTT	TCC	ATA	TCT	GTA	TCT	CTC	TTT	2544
		Leu	Thr	Asn	Leu	Ile	Leu	Phe	Ser	Leu	Ser	Ile	Ser	Val	Ser	Leu	Phe	
						815					820					825		
40		CTC	ATG	GTG	ATG	ATG	ACA	GCA	AGT	CAC	CTC	TAT	TTC	TGG	GAT	GTG	TGG	2592
		Leu	Met	Val	Met	Met	Thr	Ala	Ser	His	Leu	Tyr	Phe	Trp	Asp	Val	Trp	
						830				835					840			
45		TAT	ATT	TAC	CAT	TTC	TGT	AAG	GCC	AAG	ATA	AAG	GGG	TAT	CAG	CGT	CTA	2640
		Tyr	Ile	Tyr	His	Phe	Cys	Lys	Ala	Lys	Ile	Lys	Gly	Tyr	Gln	Arg	Leu	
				845					850					855				
50		ATA	TCA	CCA	GAC	TGT	TGC	TAT	GAT	GCT	TTT	ATT	GTG	TAT	GAC	ACT	AAA	2688
		Ile	Ser	Pro	Asp	Cys	Cys	Tyr	Asp	Ala	Phe	Ile	Val	Tyr	Asp	Thr	Lys	
			860					865					870					
55		GAC	CCA	GCT	GTG	ACC	GAG	TGG	GTT	TTG	GCT	GAG	CTG	GTG	GCC	AAA	CTG	2736
		Asp	Pro	Ala	Val	Thr	Glu	Trp	Val	Leu	Ala	Glu	Leu	Val	Ala	Lys	Leu	
		875					880					885					890	
		GAA	GAC	CCA	AGA	GAG	AAA	CAT	TTT	AAT	TTA	TGT	CTC	GAG	GAA	AGG	GAC	2784
		Glu	Asp	Pro	Arg	Glu	Lys	His	Phe	Asn	Leu	Cys	Leu	Glu	Glu	Arg	Asp	
						895					900					905		
60		TGG	TTA	CCA	GGG	CAG	CCA	GTT	CTG	GAA	AAC	CTT	TCC	CAG	AGC	ATA	CAG	2832
		Trp	Leu	Pro	Gly	Gln	Pro	Val	Leu	Glu	Asn	Leu	Ser	Gln	Ser	Ile	Gln	

	75		80		85		90									
	Gln	Ile	Lys	Pro	Arg	Ser	Phe	Ser	Gly	Leu	Thr	Tyr	Leu	Lys	Ser	Leu
					95					100					105	
5	Tyr	Leu	Asp	Gly	Asn	Gln	Leu	Leu	Glu	Ile	Pro	Gln	Gly	Leu	Pro	Pro
				110					115					120		
10	Ser	Leu	Gln	Leu	Leu	Ser	Leu	Glu	Ala	Asn	Asn	Ile	Phe	Ser	Ile	Arg
			125					130					135			
	Lys	Glu	Asn	Leu	Thr	Glu	Leu	Ala	Asn	Ile	Glu	Ile	Leu	Tyr	Leu	Gly
		140					145					150				
15	Gln	Asn	Cys	Tyr	Tyr	Arg	Asn	Pro	Cys	Tyr	Val	Ser	Tyr	Ser	Ile	Glu
	155					160					165					170
	Lys	Asp	Ala	Phe	Leu	Asn	Leu	Thr	Lys	Leu	Lys	Val	Leu	Ser	Leu	Lys
					175					180					185	
20	Asp	Asn	Asn	Val	Thr	Ala	Val	Pro	Thr	Val	Leu	Pro	Ser	Thr	Leu	Thr
				190					195					200		
	Glu	Leu	Tyr	Leu	Tyr	Asn	Asn	Met	Ile	Ala	Lys	Ile	Gln	Glu	Asp	Asp
25			205					210					215			
	Phe	Asn	Asn	Leu	Asn	Gln	Leu	Gln	Ile	Leu	Asp	Leu	Ser	Gly	Asn	Cys
	220						225					230				
30	Pro	Arg	Cys	Tyr	Asn	Ala	Pro	Phe	Pro	Cys	Ala	Pro	Cys	Lys	Asn	Asn
	235					240					245					250
	Ser	Pro	Leu	Gln	Ile	Pro	Val	Asn	Ala	Phe	Asp	Ala	Leu	Thr	Glu	Leu
					255					260					265	
35	Lys	Val	Leu	Arg	Leu	His	Ser	Asn	Ser	Leu	Gln	His	Val	Pro	Pro	Arg
				270					275					280		
	Trp	Phe	Lys	Asn	Ile	Asn	Lys	Leu	Gln	Glu	Leu	Asp	Leu	Ser	Gln	Asn
40			285					290					295			
	Phe	Leu	Ala	Lys	Glu	Ile	Gly	Asp	Ala	Lys	Phe	Leu	His	Phe	Leu	Pro
	300						305					310				
45	Ser	Leu	Ile	Gln	Leu	Asp	Leu	Ser	Phe	Asn	Phe	Glu	Leu	Gln	Val	Tyr
	315					320					325					330
	Arg	Ala	Ser	Met	Asn	Leu	Ser	Gln	Ala	Phe	Ser	Ser	Leu	Lys	Ser	Leu
				335						340					345	
50	Lys	Ile	Leu	Arg	Ile	Arg	Gly	Tyr	Val	Phe	Lys	Glu	Leu	Lys	Ser	Phe
				350					355					360		
	Asn	Leu	Ser	Pro	Leu	His	Asn	Leu	Gln	Asn	Leu	Glu	Val	Leu	Asp	Leu
55			365					370					375			
	Gly	Thr	Asn	Phe	Ile	Lys	Ile	Ala	Asn	Leu	Ser	Met	Phe	Lys	Gln	Phe
	380						385					390				
60	Lys	Arg	Leu	Lys	Val	Ile	Asp	Leu	Ser	Val	Asn	Lys	Ile	Ser	Pro	Ser
	395					400					405					410

				910				915					920				
	CTT	AGC	AAA	AAG	ACA	GTG	TTT	GTG	ATG	ACA	GAC	AAG	TAT	GCA	AAG	ACT	2880
5	Leu	Ser	Lys	Lys	Thr	Val	Phe	Val	Met	Thr	Asp	Lys	Tyr	Ala	Lys	Thr	
			925					930					935				
	GAA	AAT	TTT	AAG	ATA	GCA	TTT	TAC	TTG	TCC	CAT	CAG	AGG	CTC	ATG	GAT	2928
	Glu	Asn	Phe	Lys	Ile	Ala	Phe	Tyr	Leu	Ser	His	Gln	Arg	Leu	Met	Asp	
10			940					945				950					
	GAA	AAA	GTT	GAT	GTG	ATT	ATC	TTG	ATA	TTT	CTT	GAG	AAG	CCC	TTT	CAG	2976
	Glu	Lys	Val	Asp	Val	Ile	Ile	Leu	Ile	Phe	Leu	Glu	Lys	Pro	Phe	Gln	
			955					960				965				970	
15	AAG	TCC	AAG	TTC	CTC	CAG	CTC	CGG	AAA	AGG	CTC	TGT	GGG	AGT	TCT	GTC	3024
	Lys	Ser	Lys	Phe	Leu	Gln	Leu	Arg	Lys	Arg	Leu	Cys	Gly	Ser	Ser	Val	
					975					980					985		
20	CTT	GAG	TGG	CCA	ACA	AAC	CCG	CAA	GCT	CAC	CCA	TAC	TTC	TGG	CAG	TGT	3072
	Leu	Glu	Trp	Pro	Thr	Asn	Pro	Gln	Ala	His	Pro	Tyr	Phe	Trp	Gln	Cys	
				990					995					1000			
	CTA	AAG	AAC	GCC	CTG	GCC	ACA	GAC	AAT	CAT	GTG	GCC	TAT	AGT	CAG	GTG	3120
25	Leu	Lys	Asn	Ala	Leu	Ala	Thr	Asp	Asn	His	Val	Ala	Tyr	Ser	Gln	Val	
			1005					1010					1015				
	TTC	AAG	GAA	ACG	GTC	TAG											3138
	Phe	Lys	Glu	Thr	Val												
30			1020														

## (2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
- 35 (A) LENGTH: 1045 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
- 40

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

45	Met	Trp	Thr	Leu	Lys	Arg	Leu	Ile	Leu	Ile	Leu	Phe	Asn	Ile	Ile	Leu	
	-22		-20					-15					-10				
	Ile	Ser	Lys	Leu	Leu	Gly	Ala	Arg	Trp	Phe	Pro	Lys	Thr	Leu	Pro	Cys	
		-5					1				5					10	
50	Asp	Val	Thr	Leu	Asp	Val	Pro	Lys	Asn	His	Val	Ile	Val	Asp	Cys	Thr	
				15						20				25			
	Asp	Lys	His	Leu	Thr	Glu	Ile	Pro	Gly	Gly	Ile	Pro	Thr	Asn	Thr	Thr	
				30					35					40			
55	Asn	Leu	Thr	Leu	Thr	Ile	Asn	His	Ile	Pro	Asp	Ile	Ser	Pro	Ala	Ser	
			45				50						55				
	Phe	His	Arg	Leu	Asp	His	Leu	Val	Glu	Ile	Asp	Phe	Arg	Cys	Asn	Cys	
		60					65					70					
60	Val	Pro	Ile	Pro	Leu	Gly	Ser	Lys	Asn	Asn	Met	Cys	Ile	Lys	Arg	Leu	

Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala Arg Thr Ser Val  
 415 420 425  
 5 Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His Tyr Phe Arg Tyr  
 430 435 440  
 Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys Glu Ala Ser Phe  
 445 450 455  
 10 Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln Thr Leu Asp Leu  
 460 465 470  
 Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp Phe Gln His Leu  
 475 480 485 490  
 Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu Ile Ser Gln Thr  
 495 500 505  
 20 Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu Arg Tyr Leu Asp  
 510 515 520  
 Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr Ala Phe Glu Glu  
 525 530 535  
 25 Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn Ser His Tyr Phe  
 540 545 550  
 Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr Lys Asn Leu Lys  
 555 560 565 570  
 Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile Ser Ser Ser Thr  
 575 580 585  
 35 Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu Glu Phe Arg Gly  
 590 595 600  
 Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn Arg Tyr Leu Gln  
 605 610 615  
 40 Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp Ile Ser Lys Asn  
 620 625 630  
 Ser Leu Ser Phe Leu Pro Ser Gly Val Phe Asp Gly Met Pro Pro Asn  
 635 640 645 650  
 Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys Ser Phe Ser Trp  
 655 660 665  
 50 Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu Asp Leu Ser His  
 670 675 680  
 Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn Cys Ser Arg Ser  
 685 690 695  
 55 Leu Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg Ser Leu Thr Lys  
 700 705 710  
 Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu Asp Leu Ser Ser  
 715 720 725 730

Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro Glu Asn Val Leu  
 735 740 745  
 5 Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg Phe Leu Cys Thr  
 750 755 760  
 Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His Thr Glu Val Thr  
 765 770 775  
 10 Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly Pro Gly Ala His  
 780 785 790  
 Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr Cys Glu Leu Asp  
 795 800 805 810  
 15 Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser Val Ser Leu Phe  
 815 820 825  
 Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe Trp Asp Val Trp  
 830 835 840  
 Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly Tyr Gln Arg Leu  
 845 850 855  
 25 Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val Tyr Asp Thr Lys  
 860 865 870  
 Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu Val Ala Lys Leu  
 875 880 885 890  
 30 Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu Glu Glu Arg Asp  
 895 900 905  
 Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser Gln Ser Ile Gln  
 910 915 920  
 35 Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys Tyr Ala Lys Thr  
 925 930 935  
 40 Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln Arg Leu Met Asp  
 940 945 950  
 Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu Lys Pro Phe Gln  
 955 960 965 970  
 45 Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys Gly Ser Ser Val  
 975 980 985  
 Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro Tyr Phe Trp Gln Cys  
 990 995 1000  
 50 Leu Lys Asn Ala Leu Ala Thr Asp Asn His Val Ala Tyr Ser Gln Val  
 1005 1010 1015  
 55 Phe Lys Glu Thr Val  
 1020

(2) INFORMATION FOR SEQ ID NO:13:

60 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 180 base pairs

(B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

10 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..177

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

15	CTT GGA AAA CCT CTT CAG AAG TCT AAG TTT CTT CAG CTC AGG AAG AGA	48
	Leu Gly Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg	
	1 5 10 15	
20	CTC TGC AGG AGC TCT GTC CTT GAG TGG CCT GCA AAT CCA CAG GCT CAC	96
	Leu Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His	
	20 25 30	
25	CCA TAC TTC TGG CAG TGC CTG AAA AAT GCC CTG ACC ACA GAC AAT CAT	144
	Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn His	
	35 40 45	
30	GTG GCT TAT AGT CAA ATG TTC AAG GAA ACA GTC TAG	180
	Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val	
	50 55	

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 59 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

45	Leu Gly Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg
	1 5 10 15
50	Leu Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
	20 25 30
	Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn His
	35 40 45
	Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
	50 55

55 (2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 990 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

60

(ii) MOLECULE TYPE: cDNA

5

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 2..988

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

	G AAT TCC AGA CTT ATA AAC TTG AAA AAT CTC TAT TTG GCC TGG AAC	46
	Asn Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr Leu Ala Trp Asn	
	1 5 10 15	
15	TGC TAT TTT AAC AAA GTT TGC GAG AAA ACT AAC ATA GAA GAT GGA GTA	94
	Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile Glu Asp Gly Val	
	20 25 30	
20	TTT GAA ACG CTG ACA AAT TTG GAG TTG CTA TCA CTA TCT TTC AAT TCT	142
	Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu Ser Phe Asn Ser	
	35 40 45	
25	CTT TCA CAT GTG CCA CCC AAA CTG CCA AGC TCC CTA CGC AAA CTT TTT	190
	Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe	
	50 55 60	
30	CTG AGC AAC ACC CAG ATC AAA TAC ATT AGT GAA GAA GAT TTC AAG GGA	238
	Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu Asp Phe Lys Gly	
	65 70 75	
35	TTG ATA AAT TTA ACA TTA CTA GAT TTA AGC GGG AAC TGT CCG AGG TGC	286
	Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys	
	80 85 90 95	
40	TTC AAT GCC CCA TTT CCA TGC GTG CCT TGT GAT GGT GGT GCT TCA ATT	334
	Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly Gly Ala Ser Ile	
	100 105 110	
45	AAT ATA GAT CGT TTT GCT TTT CAA AAC TTG ACC CAA CTT CGA TAC CTA	382
	Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln Leu Arg Tyr Leu	
	115 120 125	
50	AAC CTC TCT AGC ACT TCC CTC AGG AAG ATT AAT GCT GCC TGG TTT AAA	430
	Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala Ala Trp Phe Lys	
	130 135 140	
55	AAT ATG CCT CAT CTG AAG GTG CTG GAT CTT GAA TTC AAC TAT TTA GTG	478
	Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe Asn Tyr Leu Val	
	145 150 155	
60	GGA GAA ATA GCC TCT GGG GCA TTT TTA ACG ATG CTG CCC CGC TTA GAA	526
	Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu Pro Arg Leu Glu	
	160 165 170 175	
65	ATA CTT GAC TTG TCT TTT AAC TAT ATA AAG GGG AGT TAT CCA CAG CAT	574
	Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser Tyr Pro Gln His	
	180 185 190	
70	ATT AAT ATT TCC AGA AAC TTC TCT AAA CTT TTG TCT CTA CGG GCA TTG	622
	Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser Leu Arg Ala Leu	



	195	200	205	
5	CAT TTA AGA GGT TAT GTG TTC CAG GAA CTC AGA GAA GAT GAT TTC CAG His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu Asp Asp Phe Gln 210 215 220			670
10	CCC CTG ATG CAG CTT CCA AAC TTA TCG ACT ATC AAC TTG GGT ATT AAT Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn Leu Gly Ile Asn 225 230 235			718
15	TTT ATT AAG CAA ATC GAT TTC AAA CTT TTC CAA AAT TTC TCC AAT CTG Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn Phe Ser Asn Leu 240 245 250 255			766
20	GAA ATT ATT TAC TTG TCA GAA AAC AGA ATA TCA CCG TTG GTA AAA GAT Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro Leu Val Lys Asp 260 265 270			814
25	ACC CGG CAG AGT TAT GCA AAT AGT TCC TCT TTT CAA CGT CAT ATC CGG Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln Arg His Ile Arg 275 280 285			862
30	AAA CGA CGC TCA ACA GAT TTT GAG TTT GAC CCA CAT TCG AAC TTT TAT Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His Ser Asn Phe Tyr 290 295 300			910
35	CAT TTC ACC CGT CCT TTA ATA AAG CCA CAA TGT GCT GCT TAT GGA AAA His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala Ala Tyr Gly Lys 305 310 315			958
40	GCC TTA GAT TTA AGC CTC AAC AGT ATT TTC TT Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe 320 325			990

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- 40 (A) LENGTH: 329 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## 45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Asn Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr Leu Ala Trp Asn Cys 1 5 10 15	
Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile Glu Asp Gly Val Phe 20 25 30	
Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu Ser Phe Asn Ser Leu 35 40 45	
Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu 50 55 60	
Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu Asp Phe Lys Gly Leu 65 70 75 80	

[illegible]

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1557 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS

(B) LOCATION: 1..513

(ix) FEATURE:

5

(A) NAME/KEY: misc\_feature

(B) LOCATION: 278

(D) OTHER INFORMATION: /note= "nucleotide 278 designated G, may be G or C"

(ix) FEATURE:

10

(A) NAME/KEY: misc\_feature

(B) LOCATION: 445

(D) OTHER INFORMATION: /note= "nucleotide 445 designated A, may be A or T"

15

(ix) FEATURE:

(A) NAME/KEY: misc\_feature

(B) LOCATION: 572

20

(D) OTHER INFORMATION: /note= "nucleotides 572, 593, 600, 607, 617, 622, 625, 631, 640, 646, 653, 719, 775, and 861 are designated C; each may be A, C, G, or T"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

25	CAG TCT CTT TCC ACA TCC CAA ACT TTC TAT GAT GCT TAC ATT TCT TAT	48
	Gln Ser Leu Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr	
	1 5 10 15	
30	GAC ACC AAA GAT GCC TCT GTT ACT GAC TGG GTG ATA AAT GAG CTG CGC	96
	Asp Thr Lys Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg	
	20 25 30	
35	TAC CAC CTT GAA GAG AGC CGA GAC AAA AAC GTT CTC CTT TGT CTA GAG	144
	Tyr His Leu Glu Glu Ser Arg Asp Lys Asn Val Leu Leu Cys Leu Glu	
	35 40 45	
40	GAG AGG GAT TGG GAC CCG GGA TTG GCC ATC ATC GAC AAC CTC ATG CAG	192
	Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile Ile Asp Asn Leu Met Gln	
	50 55 60	
45	AGC ATC AAC CAA AGC AAG AAA ACA GTA TTT GTT TTA ACC AAA AAA TAT	240
	Ser Ile Asn Gln Ser Lys Lys Thr Val Phe Val Leu Thr Lys Lys Tyr	
	65 70 75 80	
50	GCA AAA AGC TGG AAC TTT AAA ACA GCT TTT TAC TTG GGC TTG CAG AGG	288
	Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe Tyr Leu Gly Leu Gln Arg	
	85 90 95	
55	CTA ATG GGT GAG AAC ATG GAT GTG ATT ATA TTT ATC CTG CTG GAG CCA	336
	Leu Met Gly Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro	
	100 105 110	
60	GTG TTA CAG CAT TCT CCG TAT TTG AGG CTA CGG CAG CGG ATC TGT AAG	384
	Val Leu Gln His Ser Pro Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys	
	115 120 125	
65	AGC TCC ATC CTC CAG TGG CCT GAC AAC CCG AAG GCA GAA AGG TTG TTT	432
	Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro Lys Ala Glu Arg Leu Phe	
	130 135 140	
70	TGG CAA ACT CTG AGA AAT GTG GTC TTG ACT GAA AAT GAT TCA CGG TAT	480

	Trp	Gln	Thr	Leu	Arg	Asn	Val	Val	Leu	Thr	Glu	Asn	Asp	Ser	Arg	Tyr	
	145					150					155					160	
5	AAC	AAT	ATG	TAT	GTC	GAT	TCC	ATT	AAG	CAA	TAC	TA	ACTGACGT	TA	AGTCATGA	533	
	Asn	Asn	Met	Tyr	Val	Asp	Ser	Ile	Lys	Gln	Tyr						
					165					170							
	TTTCGCGCCA	TAATAAAGAT	GCAAAGGAAT	GACATTTCCG	TATTAGTTAT	CTATTGCTAC	593										
10	GGTAACCAAA	TTACTCCCAA	AAACCTTACG	TCGGTTTCAA	AACAACCACA	TTCTGCTGGC	653										
	CCCACAGTTT	TTGAGGGTCA	GGAGTCCAGG	CCCAGCATAA	CTGGGTCTTC	TGCTTCAGGG	713										
	TGTCTCCAGA	GGCTGCAATG	TAGGTGTTCA	CCAGAGACAT	AGGCATCACT	GGGGTCACAC	773										
15	TCCATGTGGT	TGTTTTCTGG	ATTCAATTCC	TCCTGGGCTA	TTGGCCAAAG	GCTATACTCA	833										
	TGTAAGCCAT	GCGAGCCTAT	CCCACAACGG	CAGCTTGCTT	CATCAGAGCT	AGCAAAAAAG	893										
20	AGAGGTTGCT	AGCAAGATGA	AGTCACAATC	TTTTGTAAATC	GAATCAAAAA	AGTGATATCT	953										
	CATCACTTTG	GCCATATTCT	ATTTGTTAGA	AGTAAACCAC	AGGTCCCACC	AGCTCCATGG	1013										
	GAGTGACCAC	CTCAGTCCAG	GGAAAACAGC	TGAAGACCAA	GATGGTGAGC	TCTGATTGCT	1073										
25	TCAGTTGGTC	ATCAACTATT	TTCCCTTGAC	TGCTGTCCTG	GGATGGCCGG	CTATCTTGAT	1133										
	GGATAGATTG	TGAATATCAG	GAGGCCAGGG	ATCACTGTGG	ACCATCTTAG	CAGTTGACCT	1193										
30	AACACATCTT	CTTTTCAATA	TCTAAGAACT	TTTGCCACTG	TGACTAATGG	TCCTAATATT	1253										
	AAGCTGTTGT	TTATATTTAT	CATATATCTA	TGGCTACATG	GTTATATTAT	GCTGTGGTTG	1313										
	CGTTCGGTTT	TATTTACAGT	TGCTTTTACA	AATATTTGCT	GTAACATTTG	ACTTCTAAGG	1373										
35	TTTAGATGCC	ATTTAAGAAC	TGAGATGGAT	AGCTTTTAAA	GCATCTTTTA	CTTCTTACCA	1433										
	TTTTTTAAAA	GTATGCAGCT	AAATTCGAAG	CTTTTGGTCT	ATATTGTTAA	TTGCCATTGC	1493										
40	TGTAAATCTT	AAAATGAATG	AATAAAAATG	TTTCATTTTA	AAAAAAAAAA	AAAAAAAAAA	1553										
	AAAA						1557										

45 (2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 171 amino acids

(B) TYPE: amino acid

50 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

55	Gln	Ser	Leu	Ser	Thr	Ser	Gln	Thr	Phe	Tyr	Asp	Ala	Tyr	Ile	Ser	Tyr
	1				5					10					15	
60	Asp	Thr	Lys	Asp	Ala	Ser	Val	Thr	Asp	Trp	Val	Ile	Asn	Glu	Leu	Arg
				20					25					30		

Tyr His Leu Glu Glu Ser Arg Asp Lys Asn Val Leu Leu Cys Leu Glu  
                   35                                  40                                  45  
 5 Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile Ile Asp Asn Leu Met Gln  
                   50                                  55                                  60  
 Ser Ile Asn Gln Ser Lys Lys Thr Val Phe Val Leu Thr Lys Lys Tyr  
                   65                                  70                                  75                                  80  
 10 Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe Tyr Leu Gly Leu Gln Arg  
                                   85                                  90                                  95  
 Leu Met Gly Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro  
                                   100                                  105                                  110  
 15 Val Leu Gln His Ser Pro Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys  
                                   115                                  120                                  125  
 20 Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro Lys Ala Glu Arg Leu Phe  
                   130                                  135                                  140  
 Trp Gln Thr Leu Arg Asn Val Val Leu Thr Glu Asn Asp Ser Arg Tyr  
                   145                                  150                                  155                                  160  
 25 Asn Asn Met Tyr Val Asp Ser Ile Lys Gln Tyr  
                                   165                                  170

## (2) INFORMATION FOR SEQ ID NO:19:

30 (i) SEQUENCE CHARACTERISTICS:  
       (A) LENGTH: 629 base pairs  
       (B) TYPE: nucleic acid  
       (C) STRANDEDNESS: single  
 35 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

40 (ix) FEATURE:  
       (A) NAME/KEY: CDS  
       (B) LOCATION: 1..486

45 (ix) FEATURE:  
       (A) NAME/KEY: misc\_feature  
       (B) LOCATION: 144  
       (D) OTHER INFORMATION: /note= "nucleotides 144 and 225  
       designated C; may be C or T"

50 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

AAT GAA TTG ATC CCC AAT CTA GAG AAG GAA GAT GGT TCT ATC TTG ATT	48
Asn Glu Leu Ile Pro Asn Leu Glu Lys Glu Asp Gly Ser Ile Leu Ile	
1                                  5                                  10                                  15	
55 TGC CTT TAT GAA AGC TAC TTT GAC CCT GGC AAA AGC ATT AGT GAA AAT	96
Cys Leu Tyr Glu Ser Tyr Phe Asp Pro Gly Lys Ser Ile Ser Glu Asn	
20                                  25                                  30	
60 ATT GTA AGC TTC ATT GAG AAA AGC TAT AAG TCC ATC TTT GTT TTG TCC	144
Ile Val Ser Phe Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser	

	35	40	45	
5	CCC AAC TTT GTC CAG AAT GAG TGG TGC CAT TAT GAA TTC TAC TTT GCC Pro Asn Phe Val Gln Asn Glu Trp Cys His Tyr Glu Phe Tyr Phe Ala	55	60	192
10	CAC CAC AAT CTC TTC CAT GAA AAT TCT GAT CAC ATA ATT CTT ATC TTA His His Asn Leu Phe His Glu Asn Ser Asp His Ile Ile Leu Ile Leu	65	70	240
15	CTG GAA CCC ATT CCA TTC TAT TGC ATT CCC ACC AGG TAT CAT AAA CTG Leu Glu Pro Ile Pro Phe Tyr Cys Ile Pro Thr Arg Tyr His Lys Leu	75	80	288
20	GAA GCT CTC CTG GAA AAA AAA GCA TAC TTG GAA TGG CCC AAG GAT AGG Glu Ala Leu Leu Glu Lys Lys Ala Tyr Leu Glu Trp Pro Lys Asp Arg	85	90	336
25	CGT AAA TGT GGG CTT TTC TGG GCA AAC CTT CGA GCT GCT GTT AAT GTT Arg Lys Cys Gly Leu Phe Trp Ala Asn Leu Arg Ala Ala Val Asn Val	95	100	384
30	AAT GTA TTA GCC ACC AGA GAA ATG TAT GAA CTG CAG ACA TTC ACA GAG Asn Val Leu Ala Thr Arg Glu Met Tyr Glu Leu Gln Thr Phe Thr Glu	105	110	432
35	TTA AAT GAA GAG TCT CGA GGT TCT ACA ATC TCT CTG ATG AGA ACA GAC Leu Asn Glu Glu Ser Arg Gly Ser Thr Ile Ser Leu Met Arg Thr Asp	115	120	480
40	TGT CTA TAAAATCCCA CAGTCCTTGG GAAGTTGGGG ACCACATACA CTGTTGGGAT Cys Leu	125	130	536
45	GTACATTGAT ACAACCTTTA TGATGGCAAT TTGACAATAT TTATTAAAAT AAAAAATGGT	135	140	596
50	TATTCCTTC AAAAAAAAAA AAAAAAAAAA AAA	145	150	629

40 (2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- 45 (A) LENGTH: 162 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

50	Asn Glu Leu Ile Pro Asn Leu Glu Lys Glu Asp Gly Ser Ile Leu Ile	1	5	10	15
55	Cys Leu Tyr Glu Ser Tyr Phe Asp Pro Gly Lys Ser Ile Ser Glu Asn	20	25	30	
	Ile Val Ser Phe Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser	35	40	45	
60	Pro Asn Phe Val Gln Asn Glu Trp Cys His Tyr Glu Phe Tyr Phe Ala	50	55	60	

His His Asn Leu Phe His Glu Asn Ser Asp His Ile Ile Leu Ile Leu  
 65 70 75 80  
 5 Leu Glu Pro Ile Pro Phe Tyr Cys Ile Pro Thr Arg Tyr His Lys Leu  
 85 90 95  
 Glu Ala Leu Leu Glu Lys Lys Ala Tyr Leu Glu Trp Pro Lys Asp Arg  
 100 105 110  
 10 Arg Lys Cys Gly Leu Phe Trp Ala Asn Leu Arg Ala Ala Val Asn Val  
 115 120 125  
 Asn Val Leu Ala Thr Arg Glu Met Tyr Glu Leu Gln Thr Phe Thr Glu  
 130 135 140  
 15 Leu Asn Glu Glu Ser Arg Gly Ser Thr Ile Ser Leu Met Arg Thr Asp  
 145 150 155 160  
 20 Cys Leu

## (2) INFORMATION FOR SEQ ID NO:21:

25 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 427 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

35 (ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 1..426

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

40 AAG AAC TCC AAA GAA AAC CTC CAG TTT CAT GCT TTT ATT TCA TAT AGT 48  
 Lys Asn Ser Lys Glu Asn Leu Gln Phe His Ala Phe Ile Ser Tyr Ser  
 1 5 10 15  
 45 GAA CAT GAT TCT GCC TGG GTG AAA AGT GAA TTG GTA CCT TAC CTA GAA 96  
 Glu His Asp Ser Ala Trp Val Lys Ser Glu Leu Val Pro Tyr Leu Glu  
 20 25 30  
 50 AAA GAA GAT ATA CAG ATT TGT CTT CAT GAG AGA AAC TTT GTC CCT GGC 144  
 Lys Glu Asp Ile Gln Ile Cys Leu His Glu Arg Asn Phe Val Pro Gly  
 35 40 45  
 AAG AGC ATT GTG GAA AAT ATC ATC AAC TGC ATT GAG AAG AGT TAC AAG 192  
 Lys Ser Ile Val Glu Asn Ile Ile Asn Cys Ile Glu Lys Ser Tyr Lys  
 50 55 60  
 TCC ATC TTT GTT TTG TCT CCC AAC TTT GTC CAG AGT GAG TGG TGC CAT 240  
 Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Ser Glu Trp Cys His  
 65 70 75 80  
 60 TAC GAA CTC TAT TTT GCC CAT CAC AAT CTC TTT CAT GAA GGA TCT AAT 288





(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..627

(ix) FEATURE:

(A) NAME/KEY: misc\_feature

(B) LOCATION: 54

(D) OTHER INFORMATION: /note= "nucleotides 54, 103, and 345 are designated A; each may be A or G"

(ix) FEATURE:

(A) NAME/KEY: misc\_feature

(B) LOCATION: 313

(D) OTHER INFORMATION: /note= "nucleotide 313 designated G, may be G or T"

(ix) FEATURE:

(A) NAME/KEY: misc\_feature

(B) LOCATION: 316

(D) OTHER INFORMATION: /note= "nucleotides 316, 380, 407, and 408 designated C; each may be A, C, G, or T"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GCT TCC ACC TGT GCC TGG CCT GGC TTC CCT GGC GGG GGC GGC AAA GTG	48
Ala Ser Thr Cys Ala Trp Pro Gly Phe Pro Gly Gly Gly Gly Lys Val	
1 5 10 15	
GGC GAA ATG AGG ATG CCC TGC CCT ACG ATG CCT TCG TGG TCT TCG ACA	96
Gly Glu Met Arg Met Pro Cys Pro Thr Met Pro Ser Trp Ser Ser Thr	
20 25 30	
AAA CGC AGA GCG CAG TGG CAG ACT GGG TGT ACA ACG AGC TTC GGG GGC	144
Lys Arg Arg Ala Gln Trp Gln Thr Gly Cys Thr Thr Ser Phe Gly Gly	
35 40 45	
AGC TGG AGG AGT GCC GTG GGC GCT GGG CAC TCC GCC TGT GCC TGG AGG	192
Ser Trp Arg Ser Ala Val Gly Ala Gly His Ser Ala Cys Ala Trp Arg	
50 55 60	
AAC GCG ACT GGC TGC CTG GCA AAA CCC TCT TTG AGA ACC TGT GGG CCT	240
Asn Ala Thr Gly Cys Leu Ala Lys Pro Ser Leu Arg Thr Cys Gly Pro	
65 70 75 80	
CGG TCT ATG GCA GCC GCA AGA CGC TGT TTG TGC TGG CCC ACA CGG ACC	288
Arg Ser Met Ala Ala Ala Arg Arg Cys Leu Cys Trp Pro Thr Arg Thr	
85 90 95	
GGG TCA GTG GTC TCT TGC GCG CCA GTT CTC CTG CTG GCC CAG CAG CGC	336
Gly Ser Val Val Ser Cys Ala Pro Val Leu Leu Leu Ala Gln Gln Arg	
100 105 110	
CTG CTG GAA GAC CGC AAG GAC GTC GTG GTG CTG GTG ATC CTA ACG CCT	384
Leu Leu Glu Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Thr Pro	

	115	120	125	
5	GAC GGC CAA GCC TCC CGA CTA CCC GAT GCG CTG ACC AGC GCC TCT GCC Asp Gly Gln Ala Ser Arg Leu Pro Asp Ala Leu Thr Ser Ala Ser Ala 130 135 140			432
10	GCC AGA GTG TCC TCC TCT GGC CCC ACC AGC CCA GTG GTC GCG CAG CTT Ala Arg Val Ser Ser Ser Gly Pro Thr Ser Pro Val Val Ala Gln Leu 145 150 155 160			480
	CTG AGG CCA GCA TGC ATG GCC CTG ACC AGG GAC AAC CAC CAC TTC TAT Leu Arg Pro Ala Cys Met Ala Leu Thr Arg Asp Asn His His Phe Tyr 165 170 175			528
15	AAC CGG AAC TTC TGC CAG GGA ACC CAC GGC CGA ATA GCC GTG AGC CGG Asn Arg Asn Phe Cys Gln Gly Thr His Gly Arg Ile Ala Val Ser Arg 180 185 190			576
20	AAT CCT GCA CGG TGC CAC CTC CAC ACA CAC CTA ACA TAT GCC TGC CTG Asn Pro Ala Arg Cys His Leu His Thr His Leu Thr Tyr Ala Cys Leu 195 200 205			624
25	ATC TGACCAACAC ATGCTCGCCA CCCTCACCAC ACACC Ile			662

## (2) INFORMATION FOR SEQ ID NO:24:

## 30 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 209 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## 35 (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

40	Ala Ser Thr Cys Ala Trp Pro Gly Phe Pro Gly Gly Gly Gly Lys Val 1 5 10 15
	Gly Glu Met Arg Met Pro Cys Pro Thr Met Pro Ser Trp Ser Ser Thr 20 25 30
45	Lys Arg Arg Ala Gln Trp Gln Thr Gly Cys Thr Thr Ser Phe Gly Gly 35 40 45
50	Ser Trp Arg Ser Ala Val Gly Ala Gly His Ser Ala Cys Ala Trp Arg 50 55 60
	Asn Ala Thr Gly Cys Leu Ala Lys Pro Ser Leu Arg Thr Cys Gly Pro 65 70 75 80
55	Arg Ser Met Ala Ala Ala Arg Arg Cys Leu Cys Trp Pro Thr Arg Thr 85 90 95
	Gly Ser Val Val Ser Cys Ala Pro Val Leu Leu Leu Ala Gln Gln Arg 100 105 110
60	Leu Leu Glu Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Thr Pro 115 120 125

Asp Gly Gln Ala Ser Arg Leu Pro Asp Ala Leu Thr Ser Ala Ser Ala  
130 135 140

5 Ala Arg Val Ser Ser Ser Gly Pro Thr Ser Pro Val Val Ala Gln Leu  
145 150 155 160

Leu Arg Pro Ala Cys Met Ala Leu Thr Arg Asp Asn His His Phe Tyr  
165 170 175

10 Asn Arg Asn Phe Cys Gln Gly Thr His Gly Arg Ile Ala Val Ser Arg  
180 185 190

15 Asn Pro Ala Arg Cys His Leu His Thr His Leu Thr Tyr Ala Cys Leu  
195 200 205

Ile

20 (2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 4865 base pairs  
(B) TYPE: nucleic acid  
25 (C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

30 (ix) FEATURE:  
(A) NAME/KEY: CDS  
(B) LOCATION: 107..2617

35 (ix) FEATURE:  
(A) NAME/KEY: mat\_peptide  
(B) LOCATION: 173..2617

40 (ix) FEATURE:  
(A) NAME/KEY: misc\_feature  
(B) LOCATION: 81  
(D) OTHER INFORMATION: /note= "nucleotides 81, 3144, 3205,  
and 3563 designated A, each may be A, C, G, or T"

45 (ix) FEATURE:  
(A) NAME/KEY: misc\_feature  
(B) LOCATION: 84  
(D) OTHER INFORMATION: /note= "nucleotide 84 designated C,  
may be C or G"

50 (ix) FEATURE:  
(A) NAME/KEY: misc\_feature  
(B) LOCATION: 739  
(D) OTHER INFORMATION: /note= "nucleotide 739 designated

55 C, may be C or T"

(ix) FEATURE:  
(A) NAME/KEY: misc\_feature  
(B) LOCATION: 3132  
60 (D) OTHER INFORMATION: /note= "nucleotides 3132, 3532,  
3538, and 3553 designated G, each may be G or T"

## (ix) FEATURE:

(A) NAME/KEY: misc\_feature

(B) LOCATION: 3638

5 (D) OTHER INFORMATION: /note= "nucleotide 3638 designated  
A, may be A or T"

## (ix) FEATURE:

(A) NAME/KEY: misc\_feature

(B) LOCATION: 3677

10 (D) OTHER INFORMATION: /note= "nucleotides 3677, 3685, and  
3736 designated C, each may be A or C"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

15	AAAATACTCC CTTGCCTCAA AAACGTCTCG GTCAAACGGT GATAGCAAAC CACGCATTCA	60
20	CAGGGCCACT GCTGCTCACA AAACCAGTGA GGATGATGCC AGGATG ATG TCT GCC	115
	Met Ser Ala	
	-22 -20	
25	TCG CGC CTG GCT GGG ACT CTG ATC CCA GCC ATG GCC TTC CTC TCC TGC	163
	Ser Arg Leu Ala Gly Thr Leu Ile Pro Ala Met Ala Phe Leu Ser Cys	
	-15 -10 -5	
30	GTG AGA CCA GAA AGC TGG GAG CCC TGC GTG GAG GTT CCT AAT ATT ACT	211
	Val Arg Pro Glu Ser Trp Glu Pro Cys Val Glu Val Pro Asn Ile Thr	
	1 5 10	
35	TAT CAA TGC ATG GAG CTG AAT TTC TAC AAA ATC CCC GAC AAC CTC CCC	259
	Tyr Gln Cys Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp Asn Leu Pro	
	15 20 25	
40	TTC TCA ACC AAG AAC CTG GAC CTG AGC TTT AAT CCC CTG AGG CAT TTA	307
	Phe Ser Thr Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu	
	30 35 40 45	
45	GGC AGC TAT AGC TTC TTC AGT TTC CCA GAA CTG CAG GTG CTG GAT TTA	355
	Gly Ser Tyr Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu	
	50 55 60	
50	TCC AGG TGT GAA ATC CAG ACA ATT GAA GAT GGG GCA TAT CAG AGC CTA	403
	Ser Arg Cys Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu	
	65 70 75	
55	AGC CAC CTC TCT ACC TTA ATA TTG ACA GGA AAC CCC ATC CAG AGT TTA	451
	Ser His Leu Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu	
	80 85 90	
60	GCC CTG GGA GCC TTT TCT GGA CTA TCA AGT TTA CAG AAG CTG GTG GCT	499
	Ala Leu Gly Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala	
	95 100 105	
65	GTG GAG ACA AAT CTA GCA TCT CTA GAG AAC TTC CCC ATT GGA CAT CTC	547
	Val Glu Thr Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu	
	110 115 120 125	
70	AAA ACT TTG AAA GAA CTT AAT GTG GCT CAC AAT CTT ATC CAA TCT TTC	595
	Lys Thr Leu Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe	
	130 135 140	

5	AAA TTA CCT GAG TAT TTT TCT AAT CTG ACC AAT CTA GAG CAC TTG GAC	643
	Lys Leu Pro Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp 145 150 155	
10	CTT TCC AGC AAC AAG ATT CAA AGT ATT TAT TGC ACA GAC TTG CGG GTT	691
	Leu Ser Ser Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val 160 165 170	
15	CTA CAT CAA ATG CCC CTA CTC AAT CTC TCT TTA GAC CTG TCC CTG AAC	739
	Leu His Gln Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn 175 180 185	
20	CCT ATG AAC TTT ATC CAA CCA GGT GCA TTT AAA GAA ATT AGG CTT CAT	787
	Pro Met Asn Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His 190 195 200 205	
25	AAG CTG ACT TTA AGA AAT AAT TTT GAT AGT TTA AAT GTA ATG AAA ACT	835
	Lys Leu Thr Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr 210 215 220	
30	TGT ATT CAA GGT CTG GCT GGT TTA GAA GTC CAT CGT TTG GTT CTG GGA	883
	Cys Ile Gln Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly 225 230 235	
35	GAA TTT AGA AAT GAA GGA AAC TTG GAA AAG TTT GAC AAA TCT GCT CTA	931
	Glu Phe Arg Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu 240 245 250	
40	GAG GGC CTG TGC AAT TTG ACC ATT GAA GAA TTC CGA TTA GCA TAC TTA	979
	Glu Gly Leu Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu 255 260 265	
45	GAC TAC TAC CTC GAT GAT ATT ATT GAC TTA TTT AAT TGT TTG ACA AAT	1027
	Asp Tyr Tyr Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn 270 275 280 285	
50	GTT TCT TCA TTT TCC CTG GTG AGT GTG ACT ATT GAA AGG GTA AAA GAC	1075
	Val Ser Ser Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp 290 295 300	
55	TTT TCT TAT AAT TTC GGA TGG CAA CAT TTA GAA TTA GTT AAC TGT AAA	1123
	Phe Ser Tyr Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys 305 310 315	
60	TTT GGA CAG TTT CCC ACA TTG AAA CTC AAA TCT CTC AAA AGG CTT ACT	1171
	Phe Gly Gln Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr 320 325 330	
65	TTC ACT TCC AAC AAA GGT GGG AAT GCT TTT TCA GAA GTT GAT CTA CCA	1219
	Phe Thr Ser Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro 335 340 345	
70	AGC CTT GAG TTT CTA GAT CTC AGT AGA AAT GGC TTG AGT TTC AAA GGT	1267
	Ser Leu Glu Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly 350 355 360 365	
75	TGC TGT TCT CAA AGT GAT TTT GGG ACA ACC AGC CTA AAG TAT TTA GAT	1315
	Cys Cys Ser Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp 370 375 380	

	CTG	AGC	TTC	AAT	GGT	GTT	ATT	ACC	ATG	AGT	TCA	AAC	TTC	TTG	GGC	TTA	1363
	Leu	Ser	Phe	Asn	Gly	Val	Ile	Thr	Met	Ser	Ser	Asn	Phe	Leu	Gly	Leu	
				385					390					395			
5	GAA	CAA	CTA	GAA	CAT	CTG	GAT	TTC	CAG	CAT	TCC	AAT	TTG	AAA	CAA	ATG	1411
	Glu	Gln	Leu	Glu	His	Leu	Asp	Phe	Gln	His	Ser	Asn	Leu	Lys	Gln	Met	
			400					405					410				
10	AGT	GAG	TTT	TCA	GTA	TTC	CTA	TCA	CTC	AGA	AAC	CTC	ATT	TAC	CTT	GAC	1459
	Ser	Glu	Phe	Ser	Val	Phe	Leu	Ser	Leu	Arg	Asn	Leu	Ile	Tyr	Leu	Asp	
		415					420					425					
15	ATT	TCT	CAT	ACT	CAC	ACC	AGA	GTT	GCT	TTC	AAT	GGC	ATC	TTC	AAT	GGC	1507
	Ile	Ser	His	Thr	His	Thr	Arg	Val	Ala	Phe	Asn	Gly	Ile	Phe	Asn	Gly	
	430					435					440					445	
20	TTG	TCC	AGT	CTC	GAA	GTC	TTG	AAA	ATG	GCT	GGC	AAT	TCT	TTC	CAG	GAA	1555
	Leu	Ser	Ser	Leu	Glu	Val	Leu	Lys	Met	Ala	Gly	Asn	Ser	Phe	Gln	Glu	
					450					455					460		
	AAC	TTC	CTT	CCA	GAT	ATC	TTC	ACA	GAG	CTG	AGA	AAC	TTG	ACC	TTC	CTG	1603
	Asn	Phe	Leu	Pro	Asp	Ile	Phe	Thr	Glu	Leu	Arg	Asn	Leu	Thr	Phe	Leu	
				465					470					475			
25	GAC	CTC	TCT	CAG	TGT	CAA	CTG	GAG	CAG	TTG	TCT	CCA	ACA	GCA	TTT	AAC	1651
	Asp	Leu	Ser	Gln	Cys	Gln	Leu	Glu	Gln	Leu	Ser	Pro	Thr	Ala	Phe	Asn	
			480					485					490				
30	TCA	CTC	TCC	AGT	CTT	CAG	GTA	CTA	AAT	ATG	AGC	CAC	AAC	AAC	TTC	TTT	1699
	Ser	Leu	Ser	Ser	Leu	Gln	Val	Leu	Asn	Met	Ser	His	Asn	Asn	Phe	Phe	
		495					500					505					
35	TCA	TTG	GAT	ACG	TTT	CCT	TAT	AAG	TGT	CTG	AAC	TCC	CTC	CAG	GTT	CTT	1747
	Ser	Leu	Asp	Thr	Phe	Pro	Tyr	Lys	Cys	Leu	Asn	Ser	Leu	Gln	Val	Leu	
	510					515					520					525	
40	GAT	TAC	AGT	CTC	AAT	CAC	ATA	ATG	ACT	TCC	AAA	AAA	CAG	GAA	CTA	CAG	1795
	Asp	Tyr	Ser	Leu	Asn	His	Ile	Met	Thr	Ser	Lys	Lys	Gln	Glu	Leu	Gln	
					530					535					540		
	CAT	TTT	CCA	AGT	AGT	CTA	GCT	TTC	TTA	AAT	CTT	ACT	CAG	AAT	GAC	TTT	1843
	His	Phe	Pro	Ser	Ser	Leu	Ala	Phe	Leu	Asn	Leu	Thr	Gln	Asn	Asp	Phe	
				545					550					555			
45	GCT	TGT	ACT	TGT	GAA	CAC	CAG	AGT	TTC	CTG	CAA	TGG	ATC	AAG	GAC	CAG	1891
	Ala	Cys	Thr	Cys	Glu	His	Gln	Ser	Phe	Leu	Gln	Trp	Ile	Lys	Asp	Gln	
			560					565					570				
50	AGG	CAG	CTC	TTG	GTG	GAA	GTT	GAA	CGA	ATG	GAA	TGT	GCA	ACA	CCT	TCA	1939
	Arg	Gln	Leu	Leu	Val	Glu	Val	Glu	Arg	Met	Glu	Cys	Ala	Thr	Pro	Ser	
		575					580					585					
55	GAT	AAG	CAG	GGC	ATG	CCT	GTG	CTG	AGT	TTG	AAT	ATC	ACC	TGT	CAG	ATG	1987
	Asp	Lys	Gln	Gly	Met	Pro	Val	Leu	Ser	Leu	Asn	Ile	Thr	Cys	Gln	Met	
	590					595					600					605	
60	AAT	AAG	ACC	ATC	ATT	GGT	GTG	TCG	GTC	CTC	AGT	GTG	CTT	GTA	GTA	TCT	2035
	Asn	Lys	Thr	Ile	Ile	Gly	Val	Ser	Val	Leu	Ser	Val	Leu	Val	Val	Ser	
					610					615					620		
	GTT	GTA	GCA	GTT	CTG	GTC	TAT	AAG	TTC	TAT	TTT	CAC	CTG	ATG	CTT	CTT	2083



	TATGTTATAG	CCATCATAAA	ACCATTTTGG	TAGTTTTGAC	TGAACTGGGT	GTTCAC TTTT	3027
	TCCTTTTGA	TTGAATACAA	TTTAAATTCT	ACTTGATGAC	TGCAGTCGTC	AAGGGGCTCC	3087
5	TGATGCAAGA	TGCCCCCTCC	ATTTTAAGTC	TGTCTCCTTA	CAGAGGTAA	AGTCTAATGG	3147
	CTAATTCCTA	AGGAAACCTG	ATTAACACAT	GCTCACAACC	ATCCTGGTCA	TTCTCGAACA	3207
10	TGTTCTATTT	TTTAACTAAT	CACCCCTGAT	ATATTTTTAT	TTTTATATAT	CCAGTTTCA	3267
	TTTTTTTACG	TCTTGCCAT	AAGCTAATAT	CATAAATAAG	GTTGTTTAAG	ACGTGCTTCA	3327
	AATATCCATA	TTAACCATA	TTTTTCAAGG	AAGTATGGAA	AAGTACACTC	TGTCAC TTTG	3387
15	TCAC TCGATG	TCATTCCAAA	GTTATTGCCT	ACTAAGTAAT	GA CTGTCATG	AAAGCAGCAT	3447
	TGAAATAATT	TGTTTAAAGG	GGGCACTCTT	TTAAACGGGA	AGAAAATTTT	CGCTTCCTGG	3507
20	TCTTATCATG	GACAATTTGG	GCTAGAGGCA	GGAAGGAAGT	GGGATGACCT	CAGGAAGTCA	3567
	CCTTTTCTTG	ATTCCAGAAA	CATATGGGCT	GATAAACCCG	GGGTGACCTC	ATGAAATGAG	3627
	TTGCAGCAGA	AGTTTATTTT	TTTCAGAACA	AGTGATGTTT	GATGGACCTC	TGAATCTCTT	3687
25	TAGGGAGACA	CAGATGGCTG	GGATCCCTCC	CCTGTACCCT	TCTCACTGCC	AGGAGAACTA	3747
	CGTGTGAAGG	TATTCAAGGC	AGGGAGTATA	CATTGCTGTT	TCCTGTTGGG	CAATGCTCCT	3807
30	TGACCACATT	TTGGGAAGAG	TGGATGTTAT	CATTGAGAAA	ACAATGTGTC	TGGAATTAAT	3867
	GGGGTTCTTA	TAAAGAAGGT	TCCCAGAAAA	GAATGTTTAT	TCCAGCTTCT	TCAGGAAACA	3927
	GGAACATTCA	AGGAAAAGGA	CAATCAGGAT	GTCATCAGGG	AAATGAAAAT	AAAAACCACA	3987
35	ATGAGATATC	ACCTTATACC	AGGTAGATGG	CTACTATAAA	AAAATGAAGT	GTCATCAAGG	4047
	ATATAGAGAA	ATTGGAACCC	TTCTTCACTG	CTGGAGGGAA	TGGAAAATGG	TGTAGCCGTT	4107
40	ATGAAAAACA	GTACGGAGGT	TTCTCAAAAA	TTAAAAATAG	AACTGCTATA	TGATCCAGCA	4167
	ATCTCACTTC	TGTATATATA	CCCAAAATAA	TTGAAATCAG	AATTTCAAGA	AAATATTTAC	4227
	ACTCCCATGT	TCATTGTGGC	ACTCTTCACA	ATCACTGTTT	CCAAAGTTAT	GGAAACAACC	4287
45	CAAATTTCCA	TTGGAAAATA	AATGGACAAA	GGAAATGTGC	ATATAACGTA	CAATGGGGAT	4347
	ATTATTCAGC	CTAAAAAAG	GGGGGATCCT	GTTATTTTATG	ACAACATGAA	TAAACCCGGA	4407
50	GGCCATTATG	CTATGTAAAA	TGAGCAAGTA	ACAGAAAGAC	AAATACTGCC	TGATTTTCAAT	4467
	TATATGAGGT	TCTAAAATAG	TCAAAC TCAT	AGAAGCAGAG	AATAGAACAG	TGGTTCCTAG	4527
	GGAAAAGGAG	GAAGGGAGAA	ATGAGGAAAT	AGGGAGTTGT	CTAATTGGTA	TAAAATTATA	4587
55	GTATGCAAGA	TGAATTAGCT	CTAAAGATCA	GCTGTATAGC	AGAGTTTCGTA	TAATGAACAA	4647
	TACTGTATTA	TGCACTTAAC	ATTTTGT TAA	GAGGGTACCT	CTCATGT TAA	GTGTTCTTAC	4707
60	CATATACATA	TACACAAGGA	AGCTTTTGGG	GGTGATGGAT	ATATTTATTA	CCTTGATTGT	4767
	GGTGATGGTT	TGACAGGTAT	GTGACTATGT	CTAAACTCAT	CAAATTGTAT	ACATTAAATA	4827



TATGCAGTTT TATAATATCA AAAAAAAAAA AAAAAAAAAA

4865

## 5 (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 837 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

15 Met Ser Ala Ser Arg Leu Ala Gly Thr Leu Ile Pro Ala Met Ala Phe  
-22 -20 -15 -10

20 Leu Ser Cys Val Arg Pro Glu Ser Trp Glu Pro Cys Val Glu Val Pro  
-5 1 5 10

Asn Ile Thr Tyr Gln Cys Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp  
15 20 25

25 Asn Leu Pro Phe Ser Thr Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu  
30 35 40

Arg His Leu Gly Ser Tyr Ser Phe Phe Ser Phe Pro Glu Leu Gln Val  
45 50 55

30 Leu Asp Leu Ser Arg Cys Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr  
60 65 70

35 Gln Ser Leu Ser His Leu Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile  
75 80 85 90

Gln Ser Leu Ala Leu Gly Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys  
95 100 105

40 Leu Val Ala Val Glu Thr Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile  
110 115 120

Gly His Leu Lys Thr Leu Lys Glu Leu Asn Val Ala His Asn Leu Ile  
125 130 135

45 Gln Ser Phe Lys Leu Pro Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu  
140 145 150

50 His Leu Asp Leu Ser Ser Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp  
155 160 165 170

Leu Arg Val Leu His Gln Met Pro Leu Leu Asn Leu Ser Leu Asp Leu  
175 180 185

55 Ser Leu Asn Pro Met Asn Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile  
190 195 200

Arg Leu His Lys Leu Thr Leu Arg Asn Asn Phe Asp Ser Leu Asn Val  
205 210 215

60 Met Lys Thr Cys Ile Gln Gly Leu Ala Gly Leu Glu Val His Arg Leu

	220	225	230
	Val Leu Gly Glu Phe Arg Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys		
	235	240	245 250
5	Ser Ala Leu Glu Gly Leu Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu		
		255	260 265
10	Ala Tyr Leu Asp Tyr Tyr Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys		
		270	275 280
	Leu Thr Asn Val Ser Ser Phe Ser Leu Val Ser Val Thr Ile Glu Arg		
		285	290 295
15	Val Lys Asp Phe Ser Tyr Asn Phe Gly Trp Gln His Leu Glu Leu Val		
		300	305 310
	Asn Cys Lys Phe Gly Gln Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys		
		315	320 325 330
20	Arg Leu Thr Phe Thr Ser Asn Lys Gly Gly Asn Ala Phe Ser Glu Val		
		335	340 345
	Asp Leu Pro Ser Leu Glu Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser		
		350	355 360
25	Phe Lys Gly Cys Cys Ser Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys		
		365	370 375
30	Tyr Leu Asp Leu Ser Phe Asn Gly Val Ile Thr Met Ser Ser Asn Phe		
		380	385 390
	Leu Gly Leu Glu Gln Leu Glu His Leu Asp Phe Gln His Ser Asn Leu		
		395	400 405 410
35	Lys Gln Met Ser Glu Phe Ser Val Phe Leu Ser Leu Arg Asn Leu Ile		
		415	420 425
	Tyr Leu Asp Ile Ser His Thr His Thr Arg Val Ala Phe Asn Gly Ile		
		430	435 440
40	Phe Asn Gly Leu Ser Ser Leu Glu Val Leu Lys Met Ala Gly Asn Ser		
		445	450 455
45	Phe Gln Glu Asn Phe Leu Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu		
		460	465 470
	Thr Phe Leu Asp Leu Ser Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr		
		475	480 485 490
50	Ala Phe Asn Ser Leu Ser Ser Leu Gln Val Leu Asn Met Ser His Asn		
		495	500 505
	Asn Phe Phe Ser Leu Asp Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu		
		510	515 520
55	Gln Val Leu Asp Tyr Ser Leu Asn His Ile Met Thr Ser Lys Lys Gln		
		525	530 535
60	Glu Leu Gln His Phe Pro Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln		
		540	545 550

Asn Asp Phe Ala Cys Thr Cys Glu His Gln Ser Phe Leu Gln Trp Ile  
 555 560 565 570  
 5 Lys Asp Gln Arg Gln Leu Leu Val Glu Val Glu Arg Met Glu Cys Ala  
 575 580 585  
 Thr Pro Ser Asp Lys Gln Gly Met Pro Val Leu Ser Leu Asn Ile Thr  
 590 595 600  
 10 Cys Gln Met Asn Lys Thr Ile Ile Gly Val Ser Val Leu Ser Val Leu  
 605 610 615  
 Val Val Ser Val Val Ala Val Leu Val Tyr Lys Phe Tyr Phe His Leu  
 620 625 630  
 15 Met Leu Leu Ala Gly Cys Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr  
 635 640 645 650  
 20 Asp Ala Phe Val Ile Tyr Ser Ser Gln Asp Glu Asp Trp Val Arg Asn  
 655 660 665  
 Glu Leu Val Lys Asn Leu Glu Glu Gly Val Pro Pro Phe Gln Leu Cys  
 670 675 680  
 25 Leu His Tyr Arg Asp Phe Ile Pro Gly Val Ala Ile Ala Ala Asn Ile  
 685 690 695  
 Ile His Glu Gly Phe His Lys Ser Arg Lys Val Ile Val Val Val Ser  
 700 705 710  
 30 Gln His Phe Ile Gln Ser Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala  
 715 720 725 730  
 35 Gln Thr Trp Gln Phe Leu Ser Ser Arg Ala Gly Ile Ile Phe Ile Val  
 735 740 745  
 Leu Gln Lys Val Glu Lys Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr  
 750 755 760  
 40 Arg Leu Leu Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu  
 765 770 775  
 Gly Arg His Ile Phe Trp Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly  
 780 785 790  
 45 Lys Ser Trp Asn Pro Glu Gly Thr Val Gly Thr Gly Cys Asn Trp Gln  
 795 800 805 810  
 50 Glu Ala Thr Ser Ile  
 815

## (2) INFORMATION FOR SEQ ID NO:27:

- 55 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 300 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 60 (ii) MOLECULE TYPE: cDNA

## (ix) FEATURE:

(A) NAME/KEY: CDS

5 (B) LOCATION: 1..300

## (ix) FEATURE:

(A) NAME/KEY: misc\_feature

(B) LOCATION: 186

10 (D) OTHER INFORMATION: /note= "nucleotides 186, 196, 217, 276, and 300 designated C, each may be A, C, G, or T"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

15 TCC TAT TCT ATG GAA AAA GAT GCT TTC CTA TTT ATG AGA AAT TTG AAG 48  
 Ser Tyr Ser Met Glu Lys Asp Ala Phe Leu Phe Met Arg Asn Leu Lys  
 1 5 10 15

20 GTT CTC TCA CTA AAA GAT AAC AAT GTC ACA GCT GTC CCC ACC ACT TTG 96  
 Val Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu  
 20 25 30

25 CCA CCT AAT TTA CTA GAG CTC TAT CTT TAT AAC AAT ATC ATT AAG AAA 144  
 Pro Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys  
 35 40 45

30 ATC CAA GAA AAT GAT TTC AAT AAC CTC AAT GAG TTG CAA GTC CTT GAC 192  
 Ile Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp  
 50 55 60

CTA CGT GGA AAT TGC CCT CGA TGT CAT AAT GTC CCA TAT CCG TGT ACA 240  
 Leu Arg Gly Asn Cys Pro Arg Cys His Asn Val Pro Tyr Pro Cys Thr  
 65 70 75 80

35 CCG TGT GAA AAT AAT TCC CCC TTA CAG ATC CAT GAC AAT GCT TTC AAT 288  
 Pro Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn  
 85 90 95

40 TCA TCG ACA GAC 300  
 Ser Ser Thr Asp  
 100

## 45 (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 100 amino acids

(B) TYPE: amino acid

50 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

55 Ser Tyr Ser Met Glu Lys Asp Ala Phe Leu Phe Met Arg Asn Leu Lys  
 1 5 10 15

60 Val Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu  
 20 25 30

Pro Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys  
35 40 45

Ile Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp  
5 50 55 60

Leu Arg Gly Asn Cys Pro Arg Cys His Asn Val Pro Tyr Pro Cys Thr  
65 70 75 80

10 Pro Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn.  
85 90 95

Ser Ser Thr Asp  
100

15 (2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:  
20 (A) LENGTH: 1756 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA  
25

(ix) FEATURE:  
(A) NAME/KEY: CDS  
(B) LOCATION: 1..1182  
30

(ix) FEATURE:  
(A) NAME/KEY: misc\_feature  
(B) LOCATION: 1643  
(D) OTHER INFORMATION: /note= "nucleotide 1643 designated  
35 A, may be A or G"

(ix) FEATURE:  
(A) NAME/KEY: misc\_feature  
(B) LOCATION: 1664  
40 (D) OTHER INFORMATION: /note= "nucleotide 1664 designated  
C, may be A, C, G, or T"

(ix) FEATURE:  
(A) NAME/KEY: misc\_feature  
45 (B) LOCATION: 1680  
(D) OTHER INFORMATION: /note= "nucleotides 1680 and 1735  
designated G, may be G or T"

(ix) FEATURE:  
50 (A) NAME/KEY: misc\_feature  
(B) LOCATION: 1719  
(D) OTHER INFORMATION: /note= "nucleotide 1719 designated  
C, may be C or T"

55 (ix) FEATURE:  
(A) NAME/KEY: misc\_feature  
(B) LOCATION: 1727  
(D) OTHER INFORMATION: /note= "nucleotide 1727 designated  
60 A, may be A, G, or T"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

5	TCT Ser	CCA Pro	GAA Glu	ATT Ile	CCC Pro	TGG Trp	AAT Asn	TCC Ser	TTG Leu	CCT Pro	CCT Pro	GAG Glu	GTT Val	TTT Phe	GAG Glu	GGT Gly	48
	1				5					10					15		
10	ATG Met	CCG Pro	CCA Pro	AAT Asn	CTA Leu	AAG Lys	AAT Asn	CTC Leu	TCC Ser	TTG Leu	GCC Ala	AAA Lys	AAT Asn	GGG Gly	CTC Leu	AAA Lys	96
				20					25					30			
15	TCT Ser	TTC Phe	TTT Phe	TGG Trp	GAC Asp	AGA Arg	CTC Leu	CAG Gln	TTA Leu	CTG Leu	AAG Lys	CAT His	TTG Leu	GAA Glu	ATT Ile	TTG Leu	144
			35				40						45				
20	GAC Asp	CTC Leu	AGC Ser	CAT His	AAC Asn	CAG Gln	CTG Leu	ACA Thr	AAA Lys	GTA Val	CCT Pro	GAG Glu	AGA Arg	TTG Leu	GCC Ala	AAC Asn	192
		50					55					60					
25	TGT Cys	TCC Ser	AAA Lys	AGT Ser	CTC Leu	ACA Thr	ACA Thr	CTG Leu	ATT Ile	CTT Leu	AAG Lys	CAT His	AAT Asn	CAA Gln	ATC Ile	AGG Arg	240
	65					70					75					80	
30	CAA Gln	TTG Leu	ACA Thr	AAA Lys	TAT Tyr	TTT Phe	CTA Leu	GAA Glu	GAT Asp	GCT Ala	TTG Leu	CAA Gln	TTG Leu	CGC Arg	TAT Tyr	CTA Leu	288
					85					90				95			
35	GAC Asp	ATC Ile	AGT Ser	TCA Ser	AAT Asn	AAA Lys	ATC Ile	CAG Gln	GTC Val	ATT Ile	CAG Gln	AAG Lys	ACT Thr	AGC Ser	TTC Phe	CCA Pro	336
				100					105					110			
40	GAA Glu	AAT Asn	GTC Val	CTC Leu	AAC Asn	AAT Asn	CTG Leu	GAG Glu	ATG Met	TTG Leu	GTT Val	TTA Leu	CAT His	CAC His	AAT Asn	CGC Arg	384
			115				120						125				
45	TTT Phe	CTT Leu	TGC Cys	AAC Asn	TGT Cys	GAT Asp	GCT Ala	GTG Val	TGG Trp	TTT Phe	GTC Val	TGG Trp	TGG Trp	GTT Val	AAC Asn	CAT His	432
	130						135					140					
50	ACA Thr	GAT Asp	GTT Val	ACT Thr	ATT Ile	CCA Pro	TAC Tyr	CTG Leu	GCC Ala	ACT Thr	GAT Asp	GTG Val	ACT Thr	TGT Cys	GTA Val	GGT Gly	480
	145					150					155					160	
55	CCA Pro	GGA Gly	GCA Ala	CAC His	AAA Lys	GGT Gly	CAA Gln	AGT Ser	GTC Val	ATA Ile	TCC Ser	CTT Leu	GAT Asp	CTG Leu	TAT Tyr	ACG Thr	528
					165					170				175			
60	TGT Cys	GAG Glu	TTA Leu	GAT Asp	CTC Leu	ACA Thr	AAC Asn	CTG Leu	ATT Ile	CTG Leu	TTC Phe	TCA Ser	GTT Val	TCC Ser	ATA Ile	TCA Ser	576
				180					185					190			
65	TCA Ser	GTC Val	CTC Leu	TTT Phe	CTT Leu	ATG Met	GTA Val	GTT Val	ATG Met	ACA Thr	ACA Thr	AGT Ser	CAC His	CTC Leu	TTT Phe	TTC Phe	624
			195				200						205				
70	TGG Trp	GAT Asp	ATG Met	TGG Trp	TAC Tyr	ATT Ile	TAT Tyr	TAT Tyr	TTT Phe	TGG Trp	AAA Lys	GCA Ala	AAG Lys	ATA Ile	AAG Lys	GGG Gly	672
	210						215					220					
75	TAT Tyr	CCA Pro	GCA Ala	TCT Ser	GCA Ala	ATC Ile	CCA Pro	TGG Trp	AGT Ser	CCT Pro	TGT Cys	TAT Tyr	GAT Asp	GCT Ala	TTT Phe	ATT Ile	720
	225					230					235					240	

5	GTG TAT GAC ACT AAA AAC TCA GCT GTG ACA GAA TGG GTT TTG CAG GAG	768
	Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu	
	245 250 255	
	CTG GTG GCA AAA TTG GAA GAT CCA AGA GAA AAA CAC TTC AAT TTG TGT	816
	Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys	
10	260 265 270	
	CTA GAA GAA AGA GAC TGG CTA CCA GGA CAG CCA GTT CTA GAA AAC CTT	864
	Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu	
	275 280 285	
	TCC CAG AGC ATA CAG CTC AGC AAA AAG ACA GTG TTT GTG ATG ACA CAG	912
15	Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln	
	290 295 300	
	AAA TAT GCT AAG ACT GAG AGT TTT AAG ATG GCA TTT TAT TTG TCT CAT	960
	Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His	
	305 310 315 320	
20	CAG AGG CTC CTG GAT GAA AAA GTG GAT GTG ATT ATC TTG ATA TTC TTG	1008
	Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu	
	325 330 335	
	GAA AGA CCT CTT CAG AAG TCT AAG TTT CTT CAG CTC AGG AAG AGA CTC	1056
	Glu Arg Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu	
25	340 345 350	
	TGC AGG AGC TCT GTC CTT GAG TGG CCT GCA AAT CCA CAG GCT CAC CCA	1104
	Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His Pro	
	355 360 365	
	TAC TTC TGG CAG TGC CTG AAA AAT GCC CTG ACC ACA GAC AAT CAT GTG	1152
30	Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn His Val	
	370 375 380	
	GCT TAT AGT CAA ATG TTC AAG GAA ACA GTC TAGCTCTCTG AAGAATGTCA	1202
	Ala Tyr Ser Gln Met Phe Lys Glu Thr Val	
	385 390	
35	CCACCTAGGA CATGCCTTGG TACCTGAAGT TTTCATAAAG GTTTCATAA ATGAAGGTCT	1262
	GAATTTTTC TAACAGTTGT CATGGCTCAG ATTGGTG GGA AATCATCAAT ATATGGCTAA	1322
	GAAATTAAGA AGGGGAGACT GATAGAAGAT AATTTCTTTC TTCATGTGCC ATGCTCAGTT	1382
	AAATATTTTC CCTAGCTCAA ATCTGAAAAA CTGTGCCTAG GAGACAACAC AAGGCTTTGA	1442
	TTTATCTGCA TACAATTGAT AAGAGCCACA CATCTGCCCT GAAGAAGTAC TAGTAGTTTT	1502
40	AGTAGTAGGG TAAAAATTAC ACAAGCTTTC TCTCTCTCTG ATACTGAACT GTACCAGAGT	1562
	TCAATGAAAT AAAAGCCCAG AGAACTTCTC AGTAAATGGT TTCATTATCA TGTAGTATCC	1622
	ACCATGCAAT ATGCCACAAA ACCGCTACTG GTACAGGACA GCTGGTAGCT GCTTCAAGGC	1682
	CTCTTATCAT TTTCTTGGGG CCCATGGAGG GGTCTCTCTG GAAAAAGGGA AGGTTTTTTTT	1742
	TGGCCATCCA TGAA	1756

## (2) INFORMATION FOR SEQ ID NO:30:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 394 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

10

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Ser Pro Glu Ile Pro Trp Asn Ser Leu Pro Pro Glu Val Phe Glu Gly  
 1 5 10 15  
 Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys  
 20 25 30  
 Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile Leu  
 35 40 45  
 Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala Asn  
 50 55 60  
 Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile Arg  
 65 70 75 80  
 Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr Leu  
 85 90 95  
 Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe Pro  
 100 105 110  
 Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn Arg  
 115 120 125  
 Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His  
 130 135 140  
 Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly  
 145 150 155 160  
 Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr  
 165 170 175  
 Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile Ser  
 180 185 190  
 Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe Phe  
 195 200 205  
 Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys Gly  
 210 215 220  
 Tyr Pro Ala Ser Ala Ile Pro Trp Ser Pro Cys Tyr Asp Ala Phe Ile  
 225 230 235 240  
 Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu  
 245 250 255  
 Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys



[illegible]

(2) INFORMATION FOR SEQ ID NO:31:

30 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 999 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: cDNA

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(ix) FEATURE:
      (A) NAME/KEY: CDS
40      (B) LOCATION: 2..847

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(ix) FEATURE:  
 (A) NAME/KEY: misc\_feature  
 (B) LOCATION: 4  
 (D) OTHER INFORMATION: /note= "nucleotides 4 and 23  
 designated C, each may be A, C, G, or T"

(ix) FEATURE:  
 (A) NAME/KEY: misc\_feature  
 (B) LOCATION: 650  
 (D) OTHER INFORMATION: /note= "nucleotide 650 designated  
 G, may be A or G"

55 (ix) FEATURE:  
 (A) NAME/KEY: misc\_feature  
 (B) LOCATION: 715  
 (D) OTHER INFORMATION: /note= "nucleotides 715, 825, and  
 845 designated C, each may be C or T"

60 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

	C	TCC	GAT	GCC	AAG	ATT	CGG	CAC	CAG	GCA	TAT	TCA	GAG	GTC	ATG	ATG	46
	Ser	Asp	Ala	Lys	Ile	Arg	His	Gln	Ala	Tyr	Ser	Glu	Val	Met	Met		
	1				5					10					15		
5	GTT	GGA	TGG	TCA	GAT	TCA	TAC	ACC	TGT	GAA	TAC	CCT	TTA	AAC	CTA	AGG	94
	Val	Gly	Trp	Ser	Asp	Ser	Tyr	Thr	Cys	Glu	Tyr	Pro	Leu	Asn	Leu	Arg	
				20					25					30			
10	GGA	ACT	AGG	TTA	AAA	GAC	GTT	CAT	CTC	CAC	GAA	TTA	TCT	TGC	AAC	ACA	142
	Gly	Thr	Arg	Leu	Lys	Asp	Val	His	Leu	His	Glu	Leu	Ser	Cys	Asn	Thr	
				35					40					45			
15	GCT	CTG	TTG	ATT	GTC	ACC	ATT	GTG	GTT	ATT	ATG	CTA	GTT	CTG	GGG	TTG	190
	Ala	Leu	Leu	Ile	Val	Thr	Ile	Val	Val	Ile	Met	Leu	Val	Leu	Gly	Leu	
			50					55					60				
20	GCT	GTG	GCC	TTC	TGC	TGT	CTC	CAC	TTT	GAT	CTG	CCC	TGG	TAT	CTC	AGG	238
	Ala	Val	Ala	Phe	Cys	Cys	Leu	His	Phe	Asp	Leu	Pro	Trp	Tyr	Leu	Arg	
		65					70					75					
25	ATG	CTA	GGT	CAA	TGC	ACA	CAA	ACA	TGG	CAC	AGG	GTT	AGG	AAA	ACA	ACC	286
	Met	Leu	Gly	Gln	Cys	Thr	Gln	Thr	Trp	His	Arg	Val	Arg	Lys	Thr	Thr	
	80					85				90						95	
30	CAA	GAA	CAA	CTC	AAG	AGA	AAT	GTC	CGA	TTC	CAC	GCA	TTT	ATT	TCA	TAC	334
	Gln	Glu	Gln	Leu	Lys	Arg	Asn	Val	Arg	Phe	His	Ala	Phe	Ile	Ser	Tyr	
				100					105						110		
35	AGT	GAA	CAT	GAT	TCT	CTG	TGG	GTG	AAG	AAT	GAA	TTG	ATC	CCC	AAT	CTA	382
	Ser	Glu	His	Asp	Ser	Leu	Trp	Val	Lys	Asn	Glu	Leu	Ile	Pro	Asn	Leu	
				115					120					125			
40	GAG	AAG	GAA	GAT	GGT	TCT	ATC	TTG	ATT	TGC	CTT	TAT	GAA	AGC	TAC	TTT	430
	Glu	Lys	Glu	Asp	Gly	Ser	Ile	Leu	Ile	Cys	Leu	Tyr	Glu	Ser	Tyr	Phe	
			130					135					140				
45	GAC	CCT	GGC	AAA	AGC	ATT	AGT	GAA	AAT	ATT	GTA	AGC	TTC	ATT	GAG	AAA	478
	Asp	Pro	Gly	Lys	Ser	Ile	Ser	Glu	Asn	Ile	Val	Ser	Phe	Ile	Glu	Lys	
		145					150					155					
50	AGC	TAT	AAG	TCC	ATC	TTT	GTT	TTG	TCT	CCC	AAC	TTT	GTC	CAG	AAT	GAG	526
	Ser	Tyr	Lys	Ser	Ile	Phe	Val	Leu	Ser	Pro	Asn	Phe	Val	Gln	Asn	Glu	
	160					165				170						175	
55	TGG	TGC	CAT	TAT	GAA	TTC	TAC	TTT	GCC	CAC	CAC	AAT	CTC	TTC	CAT	GAA	574
	Trp	Cys	His	Tyr	Glu	Phe	Tyr	Phe	Ala	His	His	Asn	Leu	Phe	His	Glu	
				180					185						190		
60	AAT	TCT	GAT	CAC	ATA	ATT	CTT	ATC	TTA	CTG	GAA	CCC	ATT	CCA	TTC	TAT	622
	Asn	Ser	Asp	His	Ile	Ile	Leu	Ile	Leu	Leu	Glu	Pro	Ile	Pro	Phe	Tyr	
				195					200					205			
65	TGC	ATT	CCC	ACC	AGG	TAT	CAT	AAA	CTG	GAA	GCT	CTC	CTG	GAA	AAA	AAA	670
	Cys	Ile	Pro	Thr	Arg	Tyr	His	Lys	Leu	Glu	Ala	Leu	Leu	Glu	Lys	Lys	
			210					215					220				
70	GCA	TAC	TTG	GAA	TGG	CCC	AAG	GAT	AGG	CGT	AAA	TGT	GGG	CTT	TTC	TGG	718
	Ala	Tyr	Leu	Glu	Trp	Pro	Lys	Asp	Arg	Arg	Lys	Cys	Gly	Leu	Phe	Trp	
		225					230					235					

GCA AAC CTT CGA GCT GCT GTT AAT GTT AAT GTA TTA GCC ACC AGA GAA 766  
 Ala Asn Leu Arg Ala Ala Val Asn Val Asn Val Leu Ala Thr Arg Glu  
 240 245 250 255

5 ATG TAT GAA CTG CAG ACA TTC ACA GAG TTA AAT GAA GAG TCT CGA GGT 814  
 Met Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly  
 260 265 270

10 TCT ACA ATC TCT CTG ATG AGA ACA GAC TGT CTA TAAAATCCCA CAGTCCTTGG 867  
 Ser Thr Ile Ser Leu Met Arg Thr Asp Cys Leu  
 275 280

GAAGTTGGGG ACCACATACA CTGTTGGGAT GTACATTGAT ACAACCTTTA TGATGGCAAT 927

15 TTGACAATAT TTATTAAAAT AAAAAATGGT TATTCCTTC AAAAAAAAAA AAAAAAAAAA 987  
 AAAAAAAAAA AA 999

20 (2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 282 amino acids  
 (B) TYPE: amino acid  
 25 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

30 Ser Asp Ala Lys Ile Arg His Gln Ala Tyr Ser Glu Val Met Met Val  
 1 5 10 15

35 Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg Gly  
 20 25 30

Thr Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr Ala  
 35 40 45

40 Leu Leu Ile Val Thr Ile Val Val Ile Met Leu Val Leu Gly Leu Ala  
 50 55 60

Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg Met  
 65 70 75 80

45 Leu Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr Gln  
 85 90 95

50 Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr Ser  
 100 105 110

Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu Glu  
 115 120 125

55 Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe Asp  
 130 135 140

Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys Ser  
 145 150 155 160

60 Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu Trp

165 170 175

5 Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu Asn  
180 185 190

Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr Cys  
195 200 205

10 Ile Pro Thr Arg Tyr His Lys Leu Glu Ala Leu Leu Glu Lys Lys Ala  
210 215 220

Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp Ala  
225 230 235 240

15 Asn Leu Arg Ala Ala Val Asn Val Asn Val Leu Ala Thr Arg Glu Met  
245 250 255

Tyr Glu Leu Gln Thr Phe Thr Glu Leu Asn Glu Glu Ser Arg Gly Ser  
260 265 270

20 Thr Ile Ser Leu Met Arg Thr Asp Cys Leu  
275 280

25 (2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1173 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

35 (ix) FEATURE:

- (A) NAME/KEY: CDS  
(B) LOCATION: 1..1008

40 (ix) FEATURE:

- (A) NAME/KEY: misc\_feature  
(B) LOCATION: 854  
(D) OTHER INFORMATION: /note= "nucleotide 854 designated  
A, may be A or T"

45 (ix) FEATURE:

- (A) NAME/KEY: misc\_feature  
(B) LOCATION: 1171  
(D) OTHER INFORMATION: /note= "nucleotides 1171 and 1172  
designated C, each may be A, C, G, or T"

50 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

55 CTG CCT GCT GGC ACC CGG CTC CGG AGG CTG GAT GTC AGC TGC AAC AGC 48  
Leu Pro Ala Gly Thr Arg Leu Arg Arg Leu Asp Val Ser Cys Asn Ser  
1 5 10 15

60 ATC AGC TTC GTG GCC CCC GGC TTC TTT TCC AAG GCC AAG GAG CTG CGA 96  
Ile Ser Phe Val Ala Pro Gly Phe Phe Ser Lys Ala Lys Glu Leu Arg  
20 25 30

	GAG	CTC	AAC	CTT	AGC	GCC	AAC	GCC	CTC	AAG	ACA	GTG	GAC	CAC	TCC	TGG	144
	Glu	Leu	Asn	Leu	Ser	Ala	Asn	Ala	Leu	Lys	Thr	Val	Asp	His	Ser	Trp	
			35					40					45				
5	TTT	GGG	CCC	CTG	GCG	AGT	GCC	CTG	CAA	ATA	CTA	GAT	GTA	AGC	GCC	AAC	192
	Phe	Gly	Pro	Leu	Ala	Ser	Ala	Leu	Gln	Ile	Leu	Asp	Val	Ser	Ala	Asn	
		50					55					60					
10	CCT	CTG	CAC	TGC	GCC	TGT	GGG	GCG	GCC	TTT	ATG	GAC	TTC	CTG	CTG	GAG	240
	Pro	Leu	His	Cys	Ala	Cys	Gly	Ala	Ala	Phe	Met	Asp	Phe	Leu	Leu	Glu	
		65				70					75					80	
15	GTG	CAG	GCT	GCC	GTG	CCC	GGT	CTG	CCC	AGC	CGG	GTG	AAG	TGT	GGC	AGT	288
	Val	Gln	Ala	Ala	Val	Pro	Gly	Leu	Pro	Ser	Arg	Val	Lys	Cys	Gly	Ser	
					85					90					95		
20	CCG	GGC	CAG	CTC	CAG	GGC	CTC	AGC	ATC	TTT	GCA	CAG	GAC	CTG	CGC	CTC	336
	Pro	Gly	Gln	Leu	Gln	Gly	Leu	Ser	Ile	Phe	Ala	Gln	Asp	Leu	Arg	Leu	
				100					105					110			
25	TGC	CTG	GAT	GAG	GCC	CTC	TCC	TGG	GAC	TGT	TTC	GCC	CTC	TCG	CTG	CTG	384
	Cys	Leu	Asp	Glu	Ala	Leu	Ser	Trp	Asp	Cys	Phe	Ala	Leu	Ser	Leu	Leu	
			115					120					125				
30	GCT	GTG	GCT	CTG	GGC	CTG	GGT	GTG	CCC	ATG	CTG	CAT	CAC	CTC	TGT	GGC	432
	Ala	Val	Ala	Leu	Gly	Leu	Gly	Val	Pro	Met	Leu	His	His	Leu	Cys	Gly	
		130					135					140					
35	TGG	GAC	CTC	TGG	TAC	TGC	TTC	CAC	CTG	TGC	CTG	GCC	TGG	CTT	CCC	TGG	480
	Trp	Asp	Leu	Trp	Tyr	Cys	Phe	His	Leu	Cys	Leu	Ala	Trp	Leu	Pro	Trp	
		145				150					155					160	
40	CGG	GGG	CGG	CAA	AGT	GGG	CGA	GAT	GAG	GAT	GCC	CTG	CCC	TAC	GAT	GCC	528
	Arg	Gly	Arg	Gln	Ser	Gly	Arg	Asp	Glu	Asp	Ala	Leu	Pro	Tyr	Asp	Ala	
				165					170						175		
45	TTC	GTG	GTC	TTC	GAC	AAA	ACG	CAG	AGC	GCA	GTG	GCA	GAC	TGG	GTG	TAC	576
	Phe	Val	Val	Phe	Asp	Lys	Thr	Gln	Ser	Ala	Val	Ala	Asp	Trp	Val	Tyr	
				180					185					190			
50	AAC	GAG	CTT	CGG	GGG	CAG	CTG	GAG	GAG	TGC	CGT	GGG	CGC	TGG	GCA	CTC	624
	Asn	Glu	Leu	Arg	Gly	Gln	Leu	Glu	Glu	Cys	Arg	Gly	Arg	Trp	Ala	Leu	
			195				200						205				
55	CGC	CTG	TGC	CTG	GAG	GAA	CGC	GAC	TGG	CTG	CCT	GGC	AAA	ACC	CTC	TTT	672
	Arg	Leu	Cys	Leu	Glu	Glu	Arg	Asp	Trp	Leu	Pro	Gly	Lys	Thr	Leu	Phe	
		210					215					220					
60	GAG	AAC	CTG	TGG	GCC	TCG	GTC	TAT	GGC	AGC	CGC	AAG	ACG	CTG	TTT	GTG	720
	Glu	Asn	Leu	Trp	Ala	Ser	Val	Tyr	Gly	Ser	Arg	Lys	Thr	Leu	Phe	Val	
		225				230					235					240	
65	CTG	GCC	CAC	ACG	GAC	CGG	GTC	AGT	GGT	CTC	TTG	CGC	GCC	AGC	TTC	CTG	768
	Leu	Ala	His	Thr	Asp	Arg	Val	Ser	Gly	Leu	Leu	Arg	Ala	Ser	Phe	Leu	
				245					250						255		
70	CTG	GCC	CAG	CAG	CGC	CTG	CTG	GAG	GAC	CGC	AAG	GAC	GTC	GTG	GTG	CTG	816
	Leu	Ala	Gln	Gln	Arg	Leu	Leu	Glu	Asp	Arg	Lys	Asp	Val	Val	Val	Leu	
				260					265					270			
75	GTG	ATC	CTG	AGC	CCT	GAC	GGC	CGC	CGC	TCC	CGC	TAC	GAG	CGG	CTG	CGC	864

	Val	Ile	Leu	Ser	Pro	Asp	Gly	Arg	Arg	Ser	Arg	Tyr	Glu	Arg	Leu	Arg	
			275					280					285				
5	CAG	CGC	CTC	TGC	CGC	CAG	AGT	GTC	CTC	CTC	TGG	CCC	CAC	CAG	CCC	AGT	912
	Gln	Arg	Leu	Cys	Arg	Gln	Ser	Val	Leu	Leu	Trp	Pro	His	Gln	Pro	Ser	
		290					295					300					
10	GGT	CAG	CGC	AGC	TTC	TGG	GCC	CAG	CTG	GGC	ATG	GCC	CTG	ACC	AGG	GAC	960
	Gly	Gln	Arg	Ser	Phe	Trp	Ala	Gln	Leu	Gly	Met	Ala	Leu	Thr	Arg	Asp	
	305					310				315						320	
15	AAC	CAC	CAC	TTC	TAT	AAC	CGG	AAC	TTC	TGC	CAG	GGA	CCC	ACG	GCC	GAA	1008
	Asn	His	His	Phe	Tyr	Asn	Arg	Asn	Phe	Cys	Gln	Gly	Pro	Thr	Ala	Glu	
					325					330					335		
20	TAGCCGTGAG	CCGGAATCCT	GCACGGTGCC	ACCTCCACAC	TCACCTCACC	TCTGCCTGCC											1068
	TGGTCTGACC	CTCCCCTGCT	CGCCTCCCTC	ACCCACACACC	TGACACAGAG	CAGGCACTCA											1128
20	ATAAATGCTA	CCGAAGGCTA	AAAAAAAAAA	AAAAAAAAAA	AACCA												1173

## (2) INFORMATION FOR SEQ ID NO:34:

## 25 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 336 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

## 30 (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

35	Leu	Pro	Ala	Gly	Thr	Arg	Leu	Arg	Arg	Leu	Asp	Val	Ser	Cys	Asn	Ser
	1				5					10					15	
	Ile	Ser	Phe	Val	Ala	Pro	Gly	Phe	Phe	Ser	Lys	Ala	Lys	Glu	Leu	Arg
				20				25						30		
40	Glu	Leu	Asn	Leu	Ser	Ala	Asn	Ala	Leu	Lys	Thr	Val	Asp	His	Ser	Trp
			35				40						45			
45	Phe	Gly	Pro	Leu	Ala	Ser	Ala	Leu	Gln	Ile	Leu	Asp	Val	Ser	Ala	Asn
		50					55					60				
	Pro	Leu	His	Cys	Ala	Cys	Gly	Ala	Ala	Phe	Met	Asp	Phe	Leu	Leu	Glu
	65					70				75						80
50	Val	Gln	Ala	Ala	Val	Pro	Gly	Leu	Pro	Ser	Arg	Val	Lys	Cys	Gly	Ser
					85					90					95	
	Pro	Gly	Gln	Leu	Gln	Gly	Leu	Ser	Ile	Phe	Ala	Gln	Asp	Leu	Arg	Leu
			100				105							110		
55	Cys	Leu	Asp	Glu	Ala	Leu	Ser	Trp	Asp	Cys	Phe	Ala	Leu	Ser	Leu	Leu
			115					120					125			
	Ala	Val	Ala	Leu	Gly	Leu	Gly	Val	Pro	Met	Leu	His	His	Leu	Cys	Gly
		130					135					140				
60	Trp	Asp	Leu	Trp	Tyr	Cys	Phe	His	Leu	Cys	Leu	Ala	Trp	Leu	Pro	Trp

145                      150                      155                      160  
 Arg Gly Arg Gln Ser Gly Arg Asp Glu Asp Ala Leu Pro Tyr Asp Ala  
    165                      170                      175  
 5 Phe Val Val Phe Asp Lys Thr Gln Ser Ala Val Ala Asp Trp Val Tyr  
    180                      185                      190  
 10 Asn Glu Leu Arg Gly Gln Leu Glu Glu Cys Arg Gly Arg Trp Ala Leu  
    195                      200                      205  
 Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro Gly Lys Thr Leu Phe  
    210                      215                      220  
 15 Glu Asn Leu Trp Ala Ser Val Tyr Gly Ser Arg Lys Thr Leu Phe Val  
    225                      230                      235                      240  
 Leu Ala His Thr Asp Arg Val Ser Gly Leu Leu Arg Ala Ser Phe Leu  
    245                      250                      255  
 20 Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp Val Val Val Leu  
    260                      265                      270  
 Val Ile Leu Ser Pro Asp Gly Arg Arg Ser Arg Tyr Glu Arg Leu Arg  
    275                      280                      285  
 25 Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro His Gln Pro Ser  
    290                      295                      300  
 30 Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly Met Ala Leu Thr Arg Asp  
    305                      310                      315                      320  
 Asn His His Phe Tyr Asn Arg Asn Phe Cys Gln Gly Pro Thr Ala Glu  
    325                      330                      335  
 35

## (2) INFORMATION FOR SEQ ID NO:35:

40 (i) SEQUENCE CHARACTERISTICS:  
       (A) LENGTH: 497 base pairs  
       (B) TYPE: nucleic acid  
       (C) STRANDEDNESS: single  
       (D) TOPOLOGY: linear

45 (ii) MOLECULE TYPE: cDNA

## 50 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

TGGCCACAC GGACCGCGTC AGTGGCCTCC TGCGCACCAG CTCCTGCTG GCTCAGCAGC 60  
 GCCTGTTGGA AGACCGCAAG GACGTGGTGG TGTTGGTGAT CCTGCGTCCG GATGCCCCAC 120  
 55 CGTCCCGCTA TGTGCGACTG CGCCAGCGTC TCTGCCGCCA GAGTGTGCTC TTCTGGCCCC 180  
 AGCGACCCAA CGGGCAGGGG GGCTTCTGGG CCCAGCTGAG TACAGCCCTG ACTAGGGACA 240  
 60 ACCGCCACTT CTATAACCAG AACTTCTGCC GGGGACCTAC AGCAGAATAG CTCAGAGCAA 300

CAGCTGGAAA CAGCTGCATC TTCATGTCTG GTTCCCGAGT TGCTCTGCCT GCCTTGCTCT 360  
GTCTTACTAC ACCGCTATTT GGCAAGTGCG CAATATATGC TACCAAGCCA CCAGGCCAC 420  
5 GGAGCAAAGG TTGGCTGTAA AGGGTAGTTT TCTTCCCATG CATCTTTCAG GAGAGTGAAG 480  
ATAGACACCA AACCCAC 497



## WHAT IS CLAIMED IS:

1. A substantially pure or recombinant DTLR2 protein or peptide which exhibits at least about 85% sequence  
5 identity over a length of at least about 12 amino acids to SEQ ID NO: 4.
2. A substantially pure or recombinant DTLR3 protein or peptide which exhibits at least about 85% sequence  
10 identity over a length of at least about 12 amino acids to SEQ ID NO: 6.
3. A substantially pure or recombinant DTLR4 protein or peptide which exhibits at least about 85% sequence  
15 identity over a length of at least about 12 amino acids to SEQ ID NO: 26.
4. A substantially pure or recombinant DTLR5 protein or peptide which exhibits at least about 85% sequence  
20 identity over a length of at least about 12 amino acids to SEQ ID NO: 10.
5. A substantially pure or recombinant DTLR6 protein or peptide which exhibits at least about 85% sequence  
25 identity over a length of at least about 12 amino acids to SEQ ID NO: 12.
6. A substantially pure or recombinant DTLR7 protein or peptide which exhibits at least about 85% sequence  
30 identity over a length of at least about 12 amino acids to SEQ ID NO: 16 or 18.
7. A substantially pure or recombinant DTLR8 protein or peptide which exhibits at least about 85% sequence  
35 identity over a length of at least about 12 amino acids to SEQ ID NO: 32.

8. A substantially pure or recombinant DTLR9 protein or peptide which exhibits at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 22.

5

9. A substantially pure or recombinant DTLR10 protein or peptide which exhibits at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 34.

10

10. A fusion protein comprising the protein or peptide of any of claims 1-9.

15

11. A binding compound which specifically binds to the protein or peptide of any of claims 1-9.

12. The binding compound of claim 11 which is an antibody or antibody fragment.

20

13. A nucleic acid encoding the protein or peptide of any of claims 1-9.

14.. An expression vector comprising the nucleic acid of claim 13.

25

15. A host cell comprising the vector of claim 14.

30

16. A process for recombinantly producing a polypeptide comprising culturing the host cell of claim 15 under conditions in which the polypeptide is expressed.

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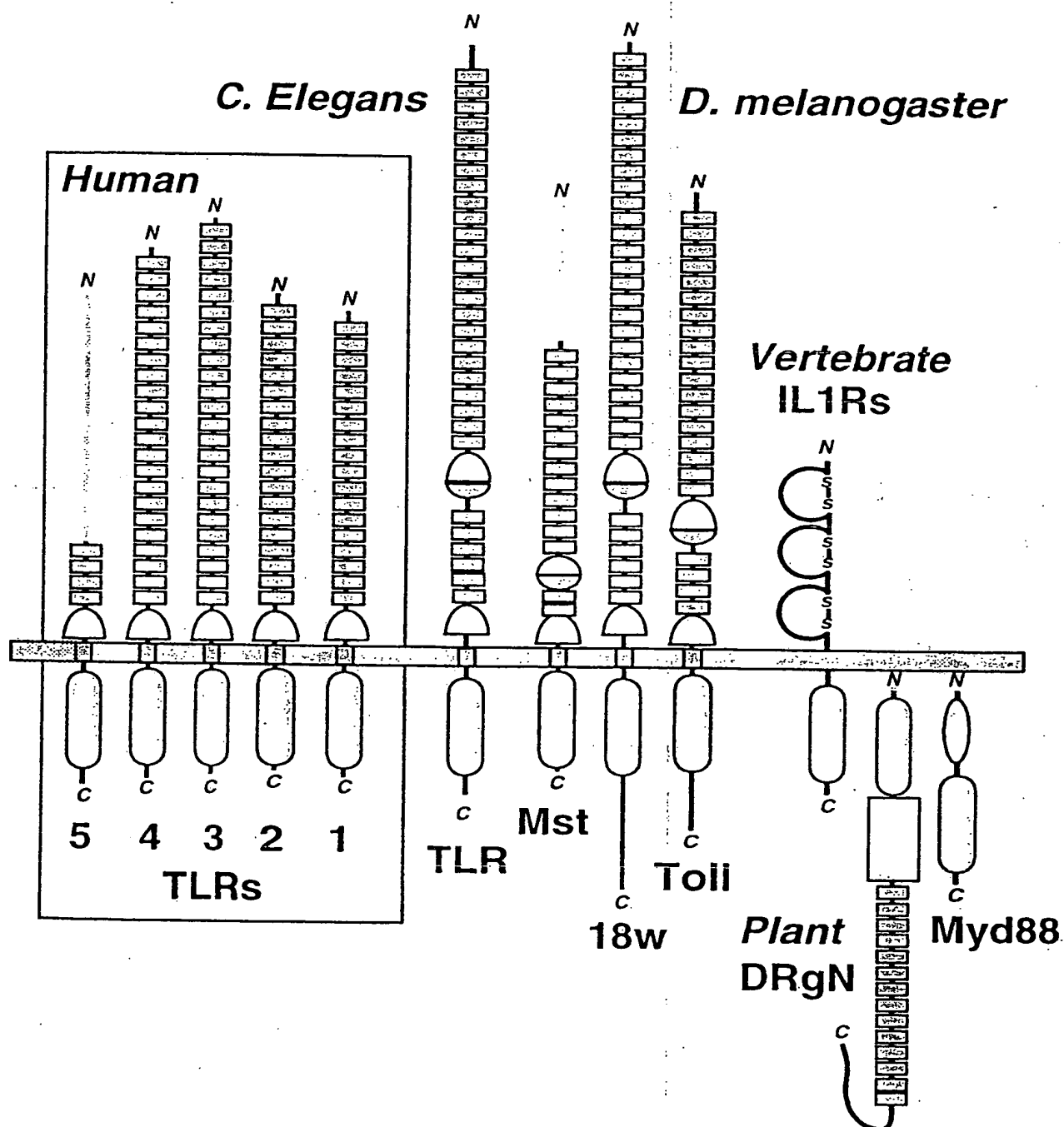


FIG. 1

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FIG. 2A

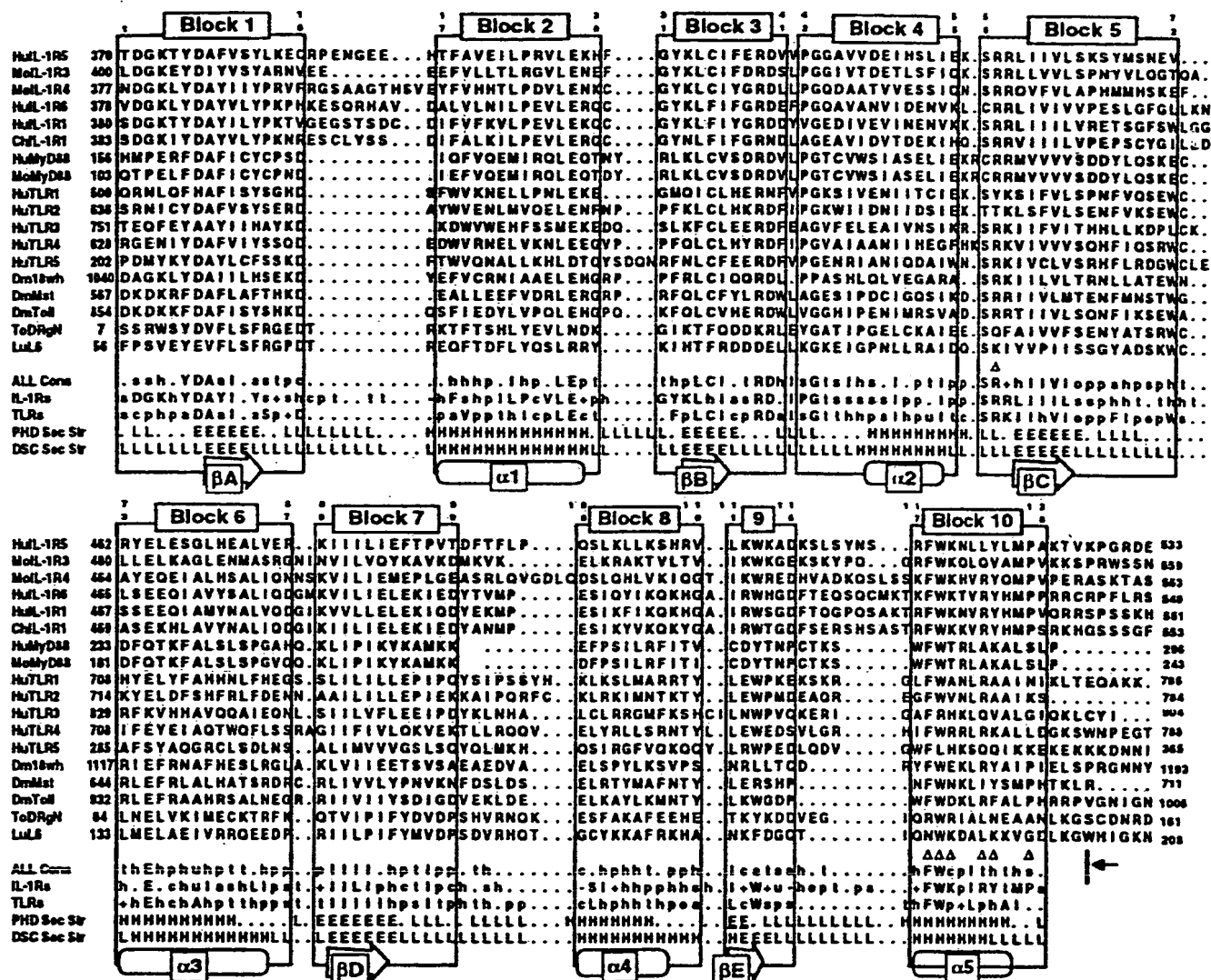
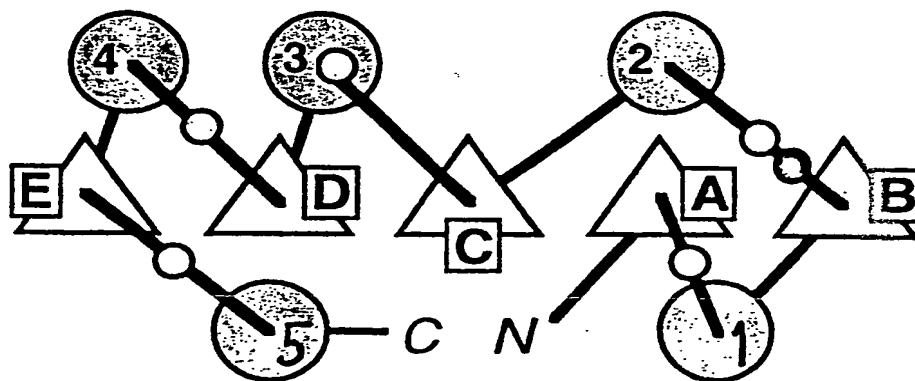


FIG. 2B



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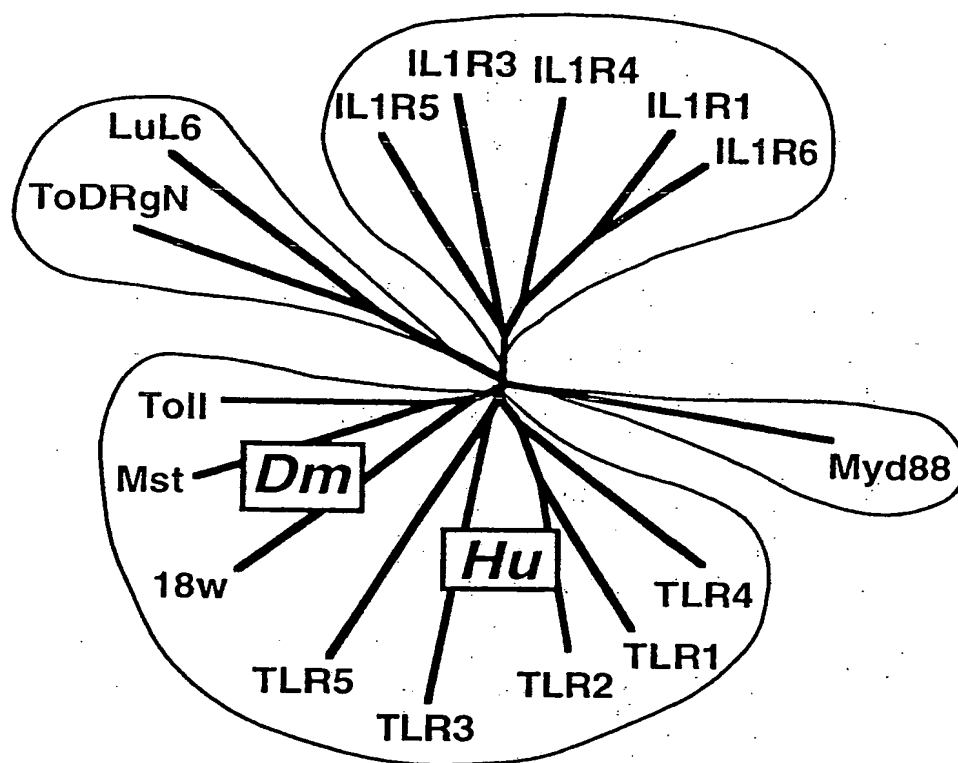


FIG. 3

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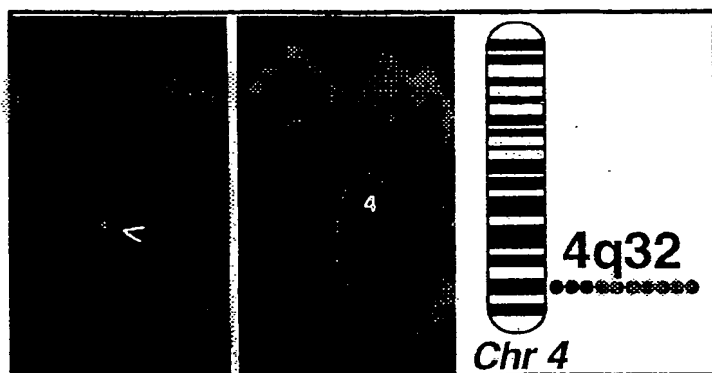


FIG. 4A

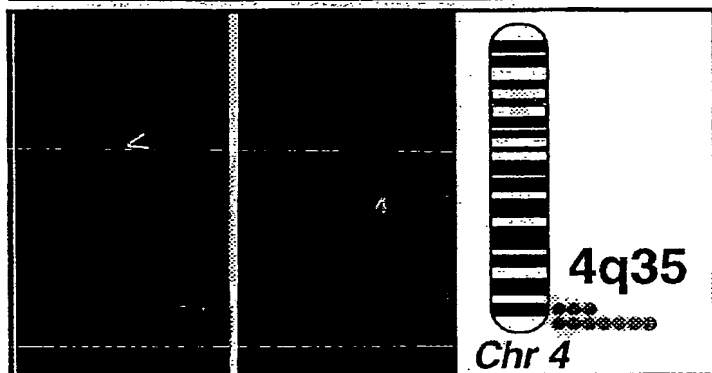


FIG. 4B

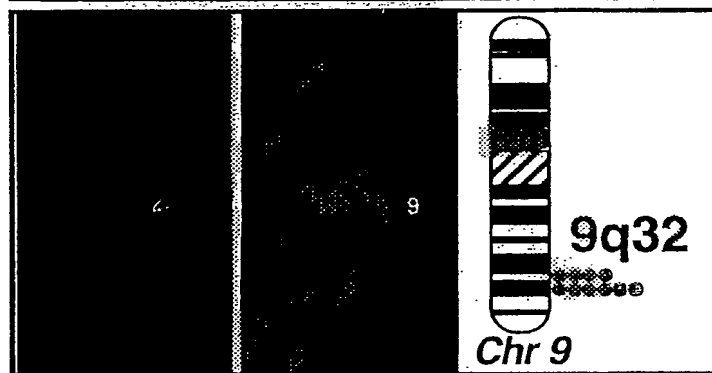


FIG. 4C

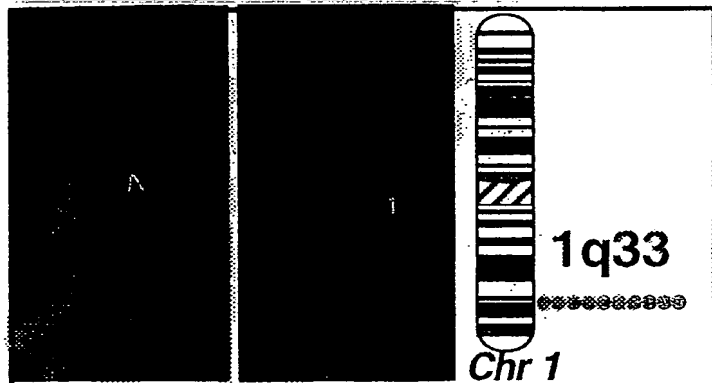


FIG. 4D

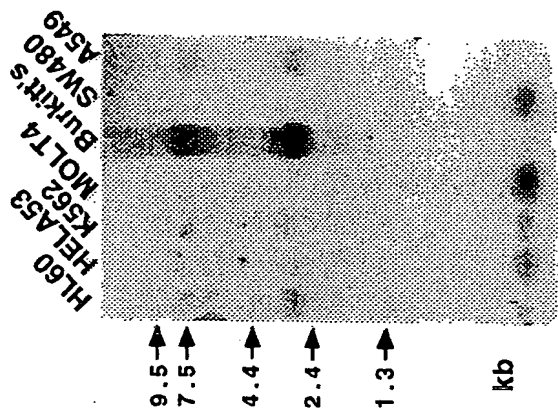


FIG. 5C

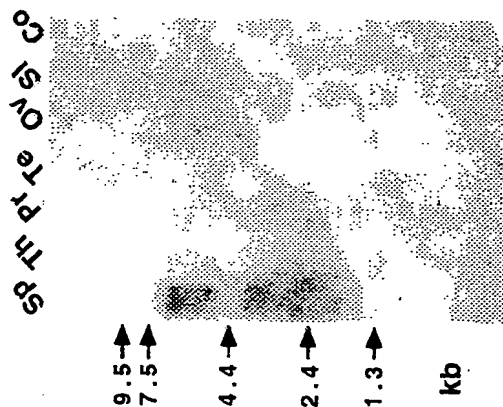


FIG. 5F

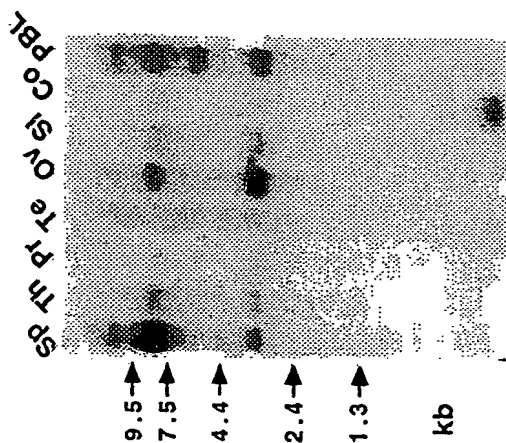


FIG. 5B

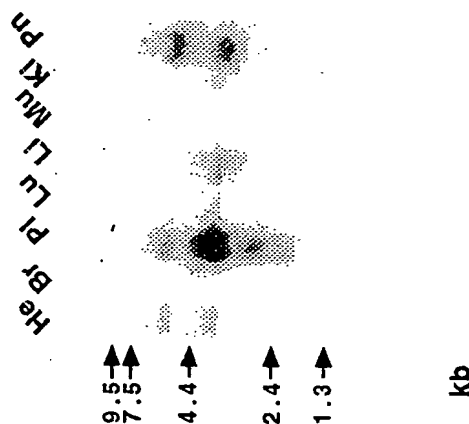


FIG. 5E

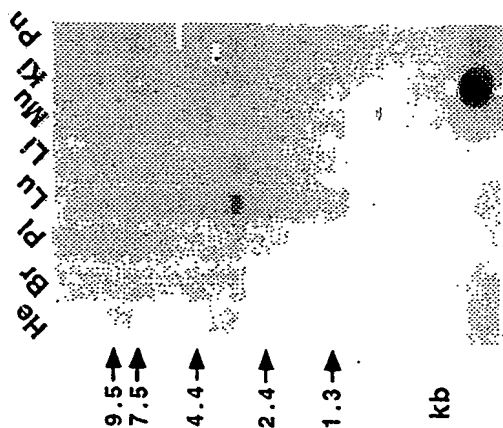


FIG. 5A

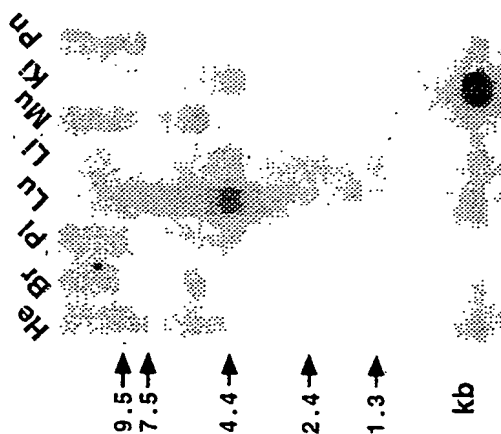


FIG. 5D

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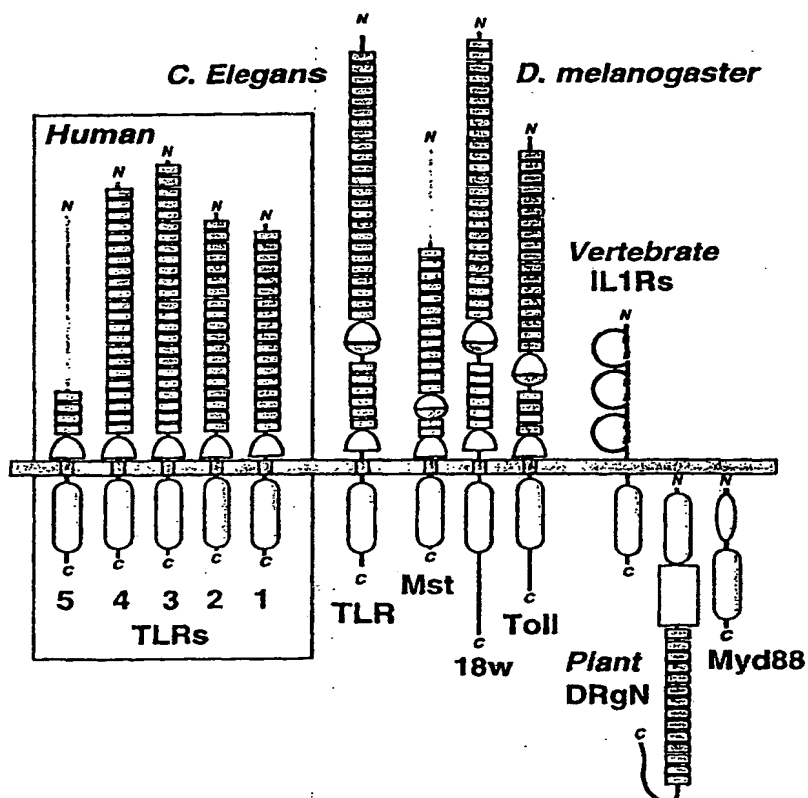
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : C12N 15/12, 15/62, C07K 14/705, 16/28, C12N 15/70		A3	(11) International Publication Number: <b>WO 98/50547</b>
			(43) International Publication Date: 12 November 1998 (12.11.98)
(21) International Application Number: PCT/US98/08979		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 7 May 1998 (07.05.98)			
(30) Priority Data: 60/044,293 7 May 1997 (07.05.97) US 60/072,212 22 January 1998 (22.01.98) US 60/076,947 5 March 1998 (05.03.98) US			
(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).		Published With international search report.	
(72) Inventors: HARDIMAN, Gerard, T.; 4 Howe Street, Watertown, MA 02172 (US). ROCK, Fernando, L.; 721 Shell Boulevard #203, Foster City, CA 94404 (US). BAZAN, J., Fernando; 775 University Drive, Menlo Park, CA 94025 (US). KASTELEIN, Robert, A.; 463 Summit Drive, Redwood City, CA 94062 (US).		(88) Date of publication of the international search report: 11 March 1999 (11.03.99)	
(74) Agents: McLAUGHLIN, Jaye, P. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).			

(54) Title: HUMAN TOLL-LIKE RECEPTOR PROTEINS, RELATED REAGENTS AND METHODS

## (57) Abstract

Nucleic acids encoding nine human receptors, designated DNAX Toll-like receptors 2-10 (DTLR2-10), homologous to the Drosophila Toll receptor and the human IL-1 receptor, purified DTLR proteins and fragments thereof, mono-/polyclonal antibodies against these receptors, and methods for diagnostic and therapeutic use.



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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/08979

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/705 C12N15/62 C07K16/28 C12N15/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NOMURA N ET AL: "PREDICTION OF THE CODING SEQUENCES OF UNIDENTIFIED HUMAN GENES I. THE CODING SEQUENCES OF 40 NEW GENES (KIAA0001-KIAA0040) DEDUCED BY ANALYSIS OF RANDOMLY SAMPLED CDNA CLONES FROM HUMAN IMMATURE MYELOID CELL LINE KG-1" DNA RESEARCH, vol. 1, no. 1, 1994, pages 27-35, XP002049267 cited in the application see page 31, left-hand column, paragraph 2; tables 2,3	1,13-16
X	-& DATABASE EMBL - EMHUM2 Entry HSRSC786, Acc.No. D13637, 31 March 1993 NOMURA, N.: "Human mRNA for KIAA0012 gene, complete cds." XP002082890 see the whole document -/--	13



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Patent family members are listed in annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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Smalt, R

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International Application No

PCT/US 98/08979

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p style="text-align: center;">---</p> <p>MEDZHITOV R ET AL: "A HUMAN HOMOLOGUE OF THE DROSOPHILA TOLL PROTEIN SIGNALS ACTIVATION OF ADAPTIVE IMMUNITY" NATURE, vol. 388, 24 July 1997, pages 394-396, XP002056592 see the whole document</p>	1,3,10, 13-16
X	<p>&amp; DATABASE EMBL - EMHUM2 Entry HSU93091, Acc.No. U93091, 11 April 1997 "Human Toll protein homolog mRNA, complete cds and LINE-1 reverse transcriptase homolog, pseudogene." XP002073841 see the whole document</p>	1,3, 13-16
X	<p style="text-align: center;">---</p> <p>DATABASE EMBL - EMBEST11 Entry HSA05049, Acc.No. AA005049, 25 July 1996 HILLIER, L. ET AL.: "zh96c04.r1 Soares fetal liver spleen INFLS S1 Homo sapiens cDNA clone 429126 5'." XP002073842 see the whole document</p>	13
X	<p style="text-align: center;">---</p> <p>DATABASE EMBL - EMBEST8 Entry HS150139, Acc.No. R76150, 10 June 1995 HILLIER, L. ET AL.: "yi71d02.r1 Homo sapiens cDNA clone 144675 5'." XP002082885 see the whole document</p>	13
X	<p style="text-align: center;">---</p> <p>DATABASE EMBL - EMBEST7 Entry HS021274, Acc.No. N41021, 27 January 1996 HILLIER, L. ET AL.: "yy53b03.s1 Homo sapiens cDNA clone 277229 3'." XP002082886 see the whole document</p>	13
X	<p style="text-align: center;">---</p> <p>DATABASE EMBL - EMBEST13 Entry HSC3991, Acc.No. C01399, 17 July 1996 OKUBO, K.: "HUMGS0008381, Human Gene Signature, 3'-direction cDNA sequence." XP002082887 see the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	13

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/08979

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ADAMS M D ET AL: "INITIAL ASSESSMENT OF HUMAN GENE DIVERSITY AND EXPRESSION PATTERNS BASED UPON 83 MILLION NUCLEOTIDES OF CDNA SEQUENCE" NATURE, vol. 377, 28 September 1995, pages 3-17, XP002042918 see the whole document	13
X	-& DATABASE EMBL - EMBEST14 Entry HSZZ86976, Acc.No. AA381849, 18 April 1997 ADAMS, M.D. ET AL.: "EST94973 Activated T-cells I Homo sapiens cDNA 5' end similar to H. sapiens hypothetical protein (GP:D13637_1)." XP002082891 see the whole document	13
X	--- DATABASE EMBL - EMBEST7 Entry HS1167131, Acc.No. AA252405, 15 March 1997 STRAUSBERG, R.: "zs12e09.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:685000 5'." XP002082888 see the whole document	13
A	--- HARDIMAN, G. ET AL.: "Molecular characterization and modular analysis of human MyD88." ONCOGENE, vol. 13, no. 11, 1996, pages 2467-75, XP002073838 see the whole document	
A	--- TAGUCHI, T. ET AL.: "Chromosomal localization of TIL, a gene encoding a protein related to the Drosophila transmembrane receptor Toll, to human chromosome 4p14" GENOMICS, vol. 32, 1996, pages 486-8, XP002073839 cited in the application see the whole document	
P,X	--- ROCK, F.L. ET AL.: "A family of human receptors structurally related to Drosophila Toll." PROC.NATL.ACAD.SCI.USA, vol. 95, January 1998, pages 588-93, XP002073840 see the whole document	1-4,7,8, 10-16
P,X	--- WO 98 02557 A (SCHERING CORP) 22 January 1998 see the whole document	1,11-16
	--- -/--	

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/08979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>DATABASE EMBL - EMHUM1                      Entry AC003046, Acc.No. AC003046,                      8 November 1997                      MUNZY, D. ET AL.: "Homo sapiens Xp22 PACs                      RPC11-263P4 and RPC11-164K3 complete                      sequence."                      XP002082889                      from bp 145453 to bp 148590.                            -----</p>	13

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 98/08979

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/08979

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, and 10-16 partially

Substantially pure recombinant DTLR2 protein or peptides which exhibit at least 85% sequence identity over a length of at least 12 amino acids to seq.4, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

2. Claims: 2, and 10-16 partially

Substantially pure recombinant DTLR3 protein or peptides which exhibit at least 85% sequence identity over a length of at least 12 amino acids to seq.6, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

3. Claims: 3, and 10-16 partially

Substantially pure recombinant DTLR4 protein or peptides which exhibit at least 85% sequence identity over a length of at least 12 amino acids to seq.26, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

4. Claims: 4, and 10-16 partially

Substantially pure recombinant DTLR5 protein or peptides which exhibit at least 85% sequence identity over a length of at least 12 amino acids to seq.10, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

5. Claims: 5, and 10-16 partially

Substantially pure recombinant DTLR6 protein or peptides which exhibit at least 85% sequence identity over a length



of at least 12 amino acids to seq.12, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

6. Claims: 6, and 10-16 partially

Substantially pure recombinant DTLR7 protein or peptides which exhibit at least 85% sequence identity over a length of at least 12 amino acids to seq.16 or 18, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

7. Claims: 7, and 10-16 partially

Substantially pure recombinant DTLR8 protein or peptides which exhibit at least 85% sequence identity over a length of at least 12 amino acids to seq.32, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

8. Claims: 8, and 10-16 partially

Substantially pure recombinant DTLR9 protein or peptides which exhibit at least 85% sequence identity over a length of at least 12 amino acids to seq.22, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

9. Claims: 9, and 10-16 partially

Substantially pure recombinant DTLR10 protein or peptides which exhibit at least 85% sequence identity over a length of at least 12 amino acids to seq.34, fusion protein comprising said protein, binding compound and/or antibody specific for said protein, nucleic acids encoding said protein, expression vector comprising the nucleic acid, host transformed with the vector, and a method for producing said peptide using the transformed host.

Human Toll-like receptors are known from e.g. Nomura et al (DNA Research 1:27-35 (1994)) (designated DTLR1 in the application), Taguchi et al (Genomics 32:486-488 (1996)), Medzhitov et al. (EMBL database Emhum2, entry HSU93091, Acc.No. U93091), and Hardiman et al (Oncogene 13(11):2467-75 (1996)).

In the light of these prior art documents, the redefined problem underlying the present application is the provision of alternative human Toll-like receptors. The solutions lie in the specific receptors, represented by SEQ. ID's 4,6,10,12,16,18,22,26,32, and 34, as described in the claimed subject matter.

In view of the prior art disclosing human Toll-like receptors, due to the essential difference in primary structure of the receptors of the various solutions, and since no other special technical feature common to these solutions can be distinguished, the ISA is of the opinion that there is no single inventive concept underlying the plurality of claimed inventions of the present application within the sense of rule 13.1 PCT. Said inventions have been formulated above as different subjects according to article 17(3)(a)PCT.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/08979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9802557 A	22-01-1998	AU 3514997 A	09-02-1998

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